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<b>(54) Title:</b> HUMAN BREAST AND OVARIAN CANCER ASSOCIATED GENE SEQUENCES AND POLYPEPTIDES			
<b>(57) Abstract</b> <p>This invention relates to newly identified breast, ovarian, breast cancer and/or ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens", and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, particularly disorders of the breast and/or ovary, including the presence of breast cancer and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, particularly disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.</p>			

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## Human Breast and Ovarian Cancer Associated Gene Sequences and Polypeptides

### 5 *Field of the Invention*

This invention relates to newly identified breast, ovarian, breast cancer, and ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens," and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such  
10 breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, specifically disorders of the breast or ovary, particularly the presence of breast and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are  
15 diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further  
20 relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.

### *Background of the Invention*

Breast cancer represents the most frequent cause of early morbidity and mortality in  
25 women in North America (Harris et al, New Eng. J. Med. 327:319, 390 and 473 (1992)). It is generally believed that this malignancy arises from a multi step process involving mutations in a relatively small number of genes, perhaps 10 or less. These mutations result in significant changes in the growth and differentiation of breast tissue that allow it to grow independent of normal cellular controls, to metastasize, and to escape immune surveillance. The genetic  
30 heterogeneity of most breast cancers suggests that they arise by a variety of initiating events

and that the characteristics of individual cancers are due to the collective pattern of genetic changes that accumulate (Harris et al. *New Eng. J. Med.* 327:319, 390 and 473 (1992)).

The classes of genes that are involved in breast cancer are not unlike those found in a number of other well characterized malignancies, although some are highly specific for breast cancer. In particular, mutations in the genes that encode receptors involved in binding to estrogen and progesterone are particularly important because they likely cause the breast cells to proliferate while rendering them unresponsive to the antitumor effects of these hormones in advanced malignancy. In addition, changes in the genes that encode growth factors, other receptors, signal transduction molecules, and transcription factor molecules are frequently involved and have alterations that are involved in the development and progression of breast cancer (King, *Nature Genetics* 2:125 (1992)). The characterization of the type and number of mutations seen in individual breast cancers is useful in classifying the biological properties of individual cancers and in determining the prognosis for individual patients. For example, the erbB2/HER2/neu gene is particularly valuable in predicting the prognosis of both node-positive and node-negative patients based on the amplification status of the gene (King, *Science* 250:1684 (1990)). Several additional members of this family have been discovered but the ligand for erbB2/HER2/neu remains unknown. It is anticipated that further advances in therapeutics will be achieved by the development of therapies that disrupt aberrant growth signaling pathways or affect the cellular interactions of breast cancer cells with native stroma or metastatic sites.

Although oncogenes are likely to be very important in breast cancer, tumor suppressor genes may also play an important role. Certain of these genes, including p53 and Rb-1, are essential to the normal mechanisms that control cell cycle events, especially those checkpoints at the border of the different stages of the cell cycle (Hollstein et al, *Science* 253:49 (1991); Srivastava et al, *Nature* 348:747 (1990)).

In 1969, Li and Fraumeni documented a familial cancer syndrome that had an autosomal dominant pattern of expression (Li et al, *Ann. Intern. Med.* 71:747 (1969)). Members of these families had sarcomas, breast cancers, brain tumors, leukemias, adrenocortical carcinomas, and other malignancies. Family studies demonstrated that the gene responsible for the syndrome was located on chromosome 17, and examination of the p53 gene as a candidate gene revealed that this gene was mutated in five families (Malsin et al, *Science* 250:1233 (1990)). In the last two years, two genes linked to familial breast cancer,

designated BRCA1 and BRCA2, have been isolated and characterized. BRCA1 is at 17q21 (Claus et al, Am. J. Epidemiology 131:961 (1990); Hall et al, Science 250:1684 (1990); Easton et al, Am. J. of Human Genetics 52 (4):678 (1993); Black et al, Am. J. of Human Genetics 52 (4):702 (1993); Bowcock et al, Am. J. of Human Genetics 52 (4):718 (1993); Miki et al, Science 266:66 (1995)). The demonstration of loss of heterozygosity (LOH) at 17q25 has defined another potential tumor suppressor gene (Lindblom et al, Human Genetics 91:6 (1993); Cornelis et al, Oncogene 8:781 (1993); Theile et al, Oncogene 10:439 (1995)).

There is a need, therefore, for identification and characterization of such factors that modulate activation and differentiation of breast and ovarian cells, both normally and in disease states. In particular, there is a need to isolate and characterize additional molecules that mediate apoptosis, DNA repair, tumor-mediated angiogenesis, genetic imprinting, immune responses to tumors and tumor antigens and, among other things, that can play a role in detecting, preventing, ameliorating or correcting dysfunctions or diseases.

The present invention relates at least in part, to a novel breast and ovarian and breast and ovarian cancer related polynucleotides and polypeptides. The discovery of these breast and ovarian cancer related polynucleotides provides new compositions which are useful in the diagnosis, prevention and treatment of disorders of the female reproductive system, particularly of the ovary including, but not limited to ovarian cancer, and the breast, including but not limited to breast cancer.

### ***Summary of the Invention***

The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of, a breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotide sequence disclosed in the sequence listing (as SEQ ID Nos:1 to 418) and/or contained in a human cDNA clone described in Tables 1, 2 and 5 and deposited with the American Type Culture Collection ("ATCC"). Fragments, variant, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes isolated nucleic acid molecules comprising, or alternatively consisting of, a polynucleotide encoding a breast, ovarian, breast cancer, and/or ovarian cancer polypeptide. The present invention further includes breast, ovarian, breast cancer, and/or ovarian cancer polypeptides encoded by these polynucleotides. Further provided for are amino acid

sequences comprising, or alternatively consisting of, breast, ovarian, breast cancer, and/or ovarian cancer polypeptides as disclosed in the sequence listing (as SEQ ID Nos: 419 to 836) and/or encoded by a human cDNA clone described in Tables 1, 2 and 5 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention.

- 5 Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides. Also provided are diagnostic methods for diagnosing and treating, preventing, and/or prognosing disorders related to the female reproductive system, specifically disorders related to the breast and/or ovary, including breast cancer  
10 and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention.

### *Detailed Description*

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#### **Tables**

- Table 1 summarizes some of the breast/ovarian cancer antigens encompassed by the invention (including contig sequences (SEQ ID NO:X) and the cDNA clone related to the contig sequence) and further summarizes certain characteristics of the breast/ovarian cancer  
20 polynucleotides and the polypeptides encoded thereby. The first column shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention. The second column provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column, "Gene Name," and the fourth column, "Overlap," provide a putative identification  
25 of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database and the database accession no. for the database sequence having similarity, respectively. The fifth and sixth columns provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as  
30 SEQ ID NO:Y. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity), respectively, observed between the aligned sequence

segments of the translation product of SEQ ID NO:X and the database sequence. The ninth column provides a unique "Clone ID" for a cDNA clone related to each contig sequence.

Table 2 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

5        Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, fifteen or more of any one or more of these public EST sequences are optionally excluded from certain embodiments of the invention.

10        Table 4 lists residues comprising antigenic epitopes of antigenic epitope-bearing fragments present in most of the breast, ovarian, breast cancer or ovarian cancer associated polynucleotides described in Table 1 as predicted by the inventors using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). Breast, ovarian, breast cancer and/or ovarian cancer associated polypeptides (e.g., SEQ ID NO:Y, polypeptides  
15        encoded by SEQ ID NO:X, or polypeptides encoded by the cDNA in the referenced cDNA clone) may possess one or more antigenic epitopes comprising residues described in Table 4. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The residues and locations shown in column two of Table 4 correspond to the amino acid sequences for most  
20        breast, ovarian, breast cancer and/or ovarian cancer associated polypeptide sequence shown in the Sequence Listing.

Table 5 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

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### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

30        In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be

"isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 1 of Table 1) or the related cDNA clone (as described in column 9 of Table 1 and contained within a library deposited with the ATCC). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown in column 9 of Table 1, each clone is identified by a cDNA Clone ID. Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 5 provides a list of the deposited cDNA libraries. One can use the Clone ID to determine the library source by reference to Tables 2 and 5. Table 5 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone ("Clone ID") isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1 correlates the Clone ID names with SEQ ID NOs. Thus, starting with a SEQ ID NO, one can use Tables 1, 2 and 5 to determine the corresponding Clone ID, from which library it came and in which ATCC deposit the library is contained. Furthermore,

it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), and/or sequences contained in the related cDNA clone within a library deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA<sup>+</sup> sequences (such as any 3' terminal polyA<sup>+</sup> tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a breast/ovarian cancer antigen polynucleotide sequence described in Table 1. SEQ ID NO:X is identified by an integer specified in column 1 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF)



encoded by polynucleotide SEQ ID NO:X. There are 418 breast/ovarian cancer antigen polynucleotide sequences described in Table 1 and shown in the sequence listing (SEQ ID NO:1 through SEQ ID NO:418). Likewise there are 418 polypeptide sequences shown in the sequence listing, one polypeptide sequence for each of the polynucleotide sequences (SEQ ID NO:419 through SEQ ID NO:836). The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:1 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:2, and so on. In other words, since there are 418 polynucleotide sequences, for any polynucleotide sequence SEQ ID NO:X, a corresponding polypeptide SEQ ID NO:Y can be determined by the formula  $X + 418 = Y$ . In addition, any of the unique "Sequence/Contig ID" defined in column 2 of Table 1, can be linked to the corresponding polypeptide SEQ ID NO:Y by reference to Table 4.

The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation,

hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to

a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

"A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

The functional activity of the breast/ovarian cancer antigen polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See

generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

#### **Breast, Ovarian, Breast Cancer and Ovarian Cancer Associated Polynucleotides and Polypeptides of the Invention**

It has been discovered herein that the polynucleotides described in Table 1 are expressed at significantly enhanced levels in human breast, ovarian, breast cancer and/or ovarian cancer tissues. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the prediction, diagnosis, prevention and treatment of disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer as more fully described below.

Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and the related cDNA clones) and further summarizes certain characteristics of these breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotides and the polypeptides encoded thereby.

Table 1

Seq ID No.	Sequence/Contig ID	Gene Name	Overlap	HGS Nucleotide Start	HGS Nucleotide End	% Identity	% Similarity	Clone ID
1	419266	monoamine oxidase B [Homo sapiens] >gil187376 monoamine oxidase B [Homo sapiens] >bbs134021 monoamine oxidase B, MAO B [human, platelet, Peptide Partial, 520 aa] [Homo sapiens] >pirJH0817JH0817 amine oxidase (flavin-containing) (EC 1.4.3.4) B - human >	gil187359	2	1021	95	95	HAGFP75
2	429114			51	383			HATDC43
3	506777			51	233			HRGCY74
4	508678	(AF059293) cytokine-like factor-1 precursor [Homo sapiens] >spJ075462J075462 CYTOKINE-LIKE FACTOR-1 PRECURSOR. Length = 422	gil3372627	3	155	100	100	HFIJG81
5	508968	DNA helicase [Homo sapiens] >pirJAS8836JAS5311 DNA helicase RECQL - human Length = 659	gil619863	2	739	95	96	HHTLH91
6	509029			770	1096			HLMDG72
7	519726			359	529			HCSSB83

8	522632		3	299		HRGBG45
9	524655		522	686		HUSGS36
10	525847	glyoxalase II [Homo sapiens] >sp Q16775 GLO2_HUMAN HYDROXYACYLGLUTATHIONE HYDROLASE (EC 3.1.2.6) (GLYOXALASE II) (GLX II). Length = 260	1	162	54	H6EDP14
11	530306		239	355		HCHCC28
12	532818	(AF035178) elongation factor 1 A2 [Oryctolagus cuniculus] >gi 38456 elongation factor 1 alpha-2 [Homo sapiens] >pir S35033 EFHUA2 translation elongation factor eEF-1 alpha-2 chain - human >sp Q05639 EF12_HUMAN ELONGATION FACTOR 1-ALPHA 2 (EF-1-ALPHA-2) (S	43	441	95	HIAMFD92
13	533385		1258	1827		HTWAO42
14	533532	actin capping protein alpha subunit [Homo sapiens] >gi 2393732 (AC002543) f-actin capping protein alpha-2 subunit [Homo sapiens] >sp P47755 CAZ2_HUMAN F- ACTIN CAPPING PROTEIN ALPHA-2 SUBUNIT (CAPZ) >gi 433308 capping protein alpha [Homo sapiens] {SUB 3-2	18	947	95	HETCD42

15	534852	(AF041472) ataxin-2 [Mus musculus] >sp O70305 O70305 SPINOCEREBELLAR ATAXIA 2 HOMOLOG (ATAXIN-2). Length = 1285 R kappa B [Homo sapiens] >pir S52863 S52863 DNA-binding protein R kappa B - human >sp Q15312 Q15312 R KAPPA B. Length = 1324	gi 3005020	3	869	77	77	HCE4Q55
16	537910		gi 695579	3	443	100	100	HTOAO52
17	538460			574	1026			HSSMY42
18	539577	transcriptional activator [Homo sapiens] >gnl PID d1005685 hSNF2b [Homo sapiens] >pir S45252 S45252 SNF2beta protein - human >gi 4056413 (AC006127) SN24_HUMAN; nuclear protein GRB1; homeotic gene regulator; SNF2-BETA [Homo sapiens] {SUB 814-1474} Length =	gi 902046	1	540	89	89	HKADQ93
19	548379	complement protein C7 precursor [Homo sapiens] >pir A27340 A27340 complement C7 precursor - human >sp P10643 CO7_HUMAN COMPLEMENT COMPONENT C7 PRECURSOR. Length = 843	gi 179716	92	1336	92	92	HATCK25
20	548489	proteasome subunit HsN3 [Homo sapiens] >pir S50147 S50147 multicatalytic endopeptidase complex (EC 3.4.99.46) beta chain N3 - human >sp P28070 PRCB_HUMAN PROTEASOME BETA CHAIN PRECURSOR (EC 3.4.99.46) (MACROPAIN BETA CHAIN)	gnl PID d100 6192	3	857	99	99	HCGAF33

## (MULTICATALYTIC ENDOPEPTIDASE

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21	548595	inosine monophosphate dehydrogenase type II [Homo sapiens] >gi 702964 inosine monophosphate dehydrogenase type II [Homo sapiens] >pir 52303 A31997 IMP dehydrogenase (EC 1.1.1.205) II - human >sp P12268 MD2_HUMAN INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE	gi 602458	971	1525	100	100	HTXEE92
22	549337	stromelysin-3 precursor [Homo sapiens] Length = 488	gi 456257	449	1081	96	96	HJMAF23
23	549777			54	293			HPMAC61
24	553091	pancreatic peptidylglycine alpha-amidating monooxygenase, PAM=membrane-bound isoform {alternatively spliced, clone PAM-3, transmembrane domain (Ba region)} [human, islet cell tumor cell line QGP-1, Peptide Partial, 971 aa] [Homo sapiens] >sp Q16252 Q16252	bbs 159681	898	2598	97	97	HEMFU73
25	553827	B-CAM gene product [Homo sapiens] >pir I37202 I37202 B-CAM protein - human Length = 588	gi 535179	2	388	80	80	HBHMI67



26	556350		263	655			HCHOC59
27	556351	'FKBP52; 52 kD FK506 binding protein' [Homo sapiens] >pir A46372 A46372 immunophilin FKBP52 - human >sp Q02790 FKB4_HUMAN P59 PROTEIN (HSP BINDING IMMUNOPHILIN) (HBI) (POSSIBLE PEPTIDYL-PROLYL CIS-TRANS ISOMERASE) (EC 5.2.1.8) (PPIASE) (ROTAMASE) (FKBP5 ubiquitin conjugating enzyme [Homo sapiens] >pir A49630 A49630 ubiquitin conjugating enzyme - human (fragment) Length = 298	2	1216	97	97	HE8DF57
28	557007	ubiquitin conjugating enzyme [Homo sapiens] >pir A49630 A49630 ubiquitin conjugating enzyme - human (fragment) Length = 298	3	698	99	100	HTEJK85
29	558140	(AD001530) putative [Homo sapiens] >sp G2335055 G2335055 XAP-5. >gnl PID d1012538 HXC-26 [Homo sapiens] {SUB 15-339} >gil 203974 XAP-5 gene product [Homo sapiens] {SUB 66-339} Length = 339	3	1070	71	71	HKAAAM18
30	558456	adipocyte lipid-binding protein [Homo sapiens] >pir A33363 FZHUUF fatty acid-binding protein, adipocyte - human >sp P15090 FABA_HUMAN FATTY ACID-BINDING PROTEIN, ADIPOCYTE (AFABP) (ADIPOCYTE LIPID-BINDING PROTEIN) (ALBP) (A-FABP). {SUB 2-132} Length = 132	69	332	100	100	HISBQ67
31	558708	N-cadherin [Homo sapiens] Length = 747	3	515	79	79	HSYBX61
32	574789		301	402			HLDNM79

33	578203			2	445			H6EDN57
34	585385	precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir A35954 A35954 endoplasmin precursor - human >sp P14625 ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803 leukocyte adhesion glycoprotein precursor [Homo sapiens] Length = 1152	gi 37261	99	347	71	71	110FMP70
35	588869		gi 307114	1	720	98	98	HDPFK39
36	597076	preferentially expressed antigen of melanoma [Homo sapiens] >sp P78395 P78395 PREFERENTIALLY EXPRESSED ANTIGEN OF MELANOMA. Length = 509	gi 1903384	80	811	77	77	HEITH66
37	598656	sigma receptor [Homo sapiens] >gi 1916800 SR31747 binding protein 1 [Homo sapiens] >gi 2914740 (AF001977) type 1 sigma receptor [Homo sapiens] >pir JC5266 JC5266 sigma receptor 1 - human >sp Q99720 Q99720 SIGMA RECEPTOR. Length = 223	gi 1783387	3	587	100	100	HMEIY05

38	611880	Acetyl-CoA:acetyltransferase (EC 2.3.1.9) (Acetoacetyl-CoA thiolase). [Escherichia coli] >gi 1788554 (AE000311) acetyl-CoA acetyltransferase [Escherichia coli] >pir F64992 F64992 hypothetical protein b2224 - Escherichia coli (strain K-12) >sp P76461 ATOB_	gn P D d 101 6745	1	108	100	100	HOVAS88
39	614329	ORF, HEIR-1; pot. neuroblastoma-associated regulator [Homo sapiens] >gi 395338 helix-loop-helix protein [Homo sapiens] >gi 512437 HEIR-1 [Homo sapiens] {SUB 30-148} Length = 148	gi 490013	300	755	86	86	HFPCCQ2
40	616066			121	213			HSIGC05
41	620956	ribosomal protein S9 [Rattus norvegicus] >pir JN0587 S21497 ribosomal protein S9 - rat Length = 194	gi 57143	3	473	95	97	HOFOB28
42	621889	unnamed protein product [unidentified] >gi 468550 CCT (chaperonin containing TCP-1) epsilon subunit [Mus musculus] >pir S43061 S43061 t-complex-type molecular chaperone Ccte - mouse Length = 541	gn P D c 3061 29	16	423	95	97	HOFOC44
43	624017	(AB003732) polyubiquitin [Cricetulus griseus] >sp O35080 O35080 POLYUBIQUITIN. >gi 4105408 (AF045474) polyubiquitin [Schistosoma mansoni] {SUB 694-988} Length = 1038	gi 2627133	1	1170	95	97	HMCBS12

44	651784	histone H2A.X [Homo sapiens] >pir S07631 S07631 histone H2A.X - human >sp P16104 H2AX_HUMAN HISTONE H2A.X. {SUB 2-143} Length = 143	gi 31973	2	514	98	98	HKGA194
45	651826	keratin, 55K type II cytoskeletal - human (fragment) Length = 489	pir B24177 B 24177	2	1300	86	86	HNTAH42
46	653282	phosphate transfer protein B precursor, mitochondrial - bovine Length = 361	pir D53737 D 53737	30	392	90	90	HOFNY90
47	657122			1	204			IKGAQ13
48	661442	rab1B protein (AA 1 - 201) [Rattus sp.] Length = 201	gi 57006	1	672	98	99	IICHM133
49	664914	phosphotyrosyl phosphatase activator [Oryctolagus cuniculus] >pir B54021 B54021 phosphotyrosyl phosphatase activator PTPA - rabbit >sp Q28717 Q28717 PHOSPHOTYROSYL PHOSPHATASE ACTIVATOR. Length = 323	gi 509144	1	228	98	100	HIEGAK11
50	666654			63	395			HOFNL37
51	667084	cytokeratin 17 [Homo sapiens] >gi 34075 keratin related product [Homo sapiens] >pir S30433 S30433 keratin 17, cytoskeletal - human >sp Q04695 K1CQ_HUMAN KERATIN, TYPE I CYTOSKELETAL 17 (CYTOKERATIN 17) (K17) (CK 17) (39.1) (VERSION 1). {SUB 2-432} Length	gi 30379	3	1379	100	100	HKADA74

52	667380	cell surface glycoprotein [Homo sapiens] >gnl PID d1006754 TALLA-1 [Homo sapiens] >gnl PID d1001976 cell surface glycoprotein [Homo sapiens] >pir 39368 39368 T-cell acute lymphoblastic leukemia associated antigen 1 - human >sp P41732 A15_HUMAN CELL SURF	gnl PID d1001976	1	474	100	100	HMIBK53
53	669530			264	440			HPFCJ30
54	671315	cell cycle checkpoint control protein [Homo sapiens] >sp Q99638 Q99638 CELL CYCLE CHECKPOINT CONTROL PROTEIN. Length = 391	gil1765956	320	1279	92	92	HDA BE95
55	671993	NAD(H)-specific isocitrate dehydrogenase gamma-subunit precursor [Homo sapiens] >gnl PID e219959 NAD (H)-specific isocitrate dehydrogenase gamma subunit precursor [Homo sapiens] >gil1302655 NAD+-isocitrate dehydrogenase gamma subunit [Homo sapiens] >gil40	gnl PID e211919	1	993	91	91	HSJCA89
56	674618			223	312			HOVBX22
57	675027			789	1160			HSDII69
58	677202	vimentin [Homo sapiens] >sp Q15867 Q15867 VIMENTIN (FRAGMENT). Length = 354	gil340232	705	896	100	100	HWACG51

59	678504	ORF YGR031w [Saccharomyces cerevisiae] >pir[S64322]S64322 probable membrane protein YGR031w - yeast (Saccharomyces cerevisiae) Length = 342	gnl PIDe243277	320	640	38	63	HCHAG27
60	678985	54 kDa protein [Homo sapiens] >gnl PIDe1245514 p54nrb [Homo sapiens] >pir G01211 G01211 54 kDa protein - human >sp Q12786 Q12786 54 KDA PROTEIN. Length = 471	gi 407308	358	1203	100	100	HCHOL54
61	682161	(AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi 3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358	gi 2920585	3	869	89	89	HCHAG19
62	683476			1	132			HOFMM27
63	691146	KDEL receptor [Homo sapiens] >pir S13293 S13293 KDEL receptor - human >sp P24390 ER21_HUMAN ER LUMEN PROTEIN RETAINING RECEPTOR 1 (KDEL RECEPTOR 1). Length = 212	gi 34031	1	372	100	100	IIDAIBB02
64	693589			1	393			HCHAS12

65	694991	B4B gene product [Homo sapiens] >gnl PID e265628 progression associated protein [Homo sapiens] >gil 932786 epithelial membrane protein [Homo sapiens] >gil2506160 TMP [Homo sapiens] >sp P54849 EMPI_HUMAN EPITHELIAL MEMBRANE PROTEIN-1 (EMP-1) (TUMOR-ASSOCIA	gnl PID e1949 46	1	663	98	98	98	HIRAAAY77
66	698303	heat shock factor 1 [Homo sapiens] >pir A41137 A41137 heat shock transcription factor 1 - human >sp Q00613 HSF1_HUMAN HEAT SHOCK FACTOR PROTEIN 1 (HSF 1) (HEAT SHOCK TRANSCRIPTION FACTOR 1) (HSTF 1). Length = 529 filamin [Homo sapiens] Length = 2647	gil 84403	23	1168	85	85	85	HSHCA55
67	698669		gil 203969	27	1274	98	98	98	HEGAR20
68	705696			321	458				HOFMP28
69	706393	vacuolar H+ ATPase proton channel subunit [Homo sapiens] >pir A39367 A39367 H+- transporting ATPase (EC 3.6.1.35) chain PKD1 - human Length = 155	gil 89676	119	604	84	84	85	HSKHP64
70	707357			3	344				HOFMM35

71	707360	leucine aminopeptidase, LAP [cattle, kidney, Peptide, 513 aa] [Bos taurus] >pir A54338 APBOL leucyl aminopeptidase (EC 3.4.11.1), renal - bovine >sp P00727 AMPL_BOVIN CYTOSOL AMINOPEPTIDASE (EC 3.4.11.1) (LEUCINE AMINOPEPTIDASE) (LAP) (LEUCYL AMINOPEPTIDASE) serine/threonine protein kinase [Homo sapiens] >pir S23385 S23385 protein kinase (EC 2.7.1.37) cdc2-related PCTAIRE-1 - human >sp Q00536 KPT1_HUMAN SERINE/THREONINE-PROTEIN KINASE PCTAIRE-1 (EC 2.7.1.-) >sp G252370 G252370 CDC2-RELATED PROTEIN KINASE {CL	bbs 137417	1	447	81	89	HOFOF35
72	707375		gij36619	2	1582	92	92	H1OJOQ73
73	707754			2	376			HLDBT45
74	711172			237	395			HOVC140
75	712248	transcription factor AP-2 beta [Homo sapiens] >sp E286536 E286536 TRANSCRIPTION FACTOR AP-2 BETA. Length = 367	gnl PID e286536	99	344	100	100	HKGCW94
76	715445	DNA-PK [Homo sapiens] >pir G02083 G02083 DNA-PK - human (fragment) >sp Q13337 Q13337 DNA-PK (FRAGMENT). Length = 930	gij1017757	119	988	99	99	HL1DJ07
77	716362			221	688			H1BGC77



78	716835	(AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi 3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358	gi 2920585	3	755	79	79	HCHAI81
79	716947	SRp55-2 [Homo sapiens] Length = 135	gi 1049084	2	145	100	100	HADDY71
80	717685	alpha-mannosidase [Homo sapiens] Length = 987	gi 1419374	2	1120	99	99	HIDPUO15
81	719755			89	802			HCGACS4
82	720389	inducible membrane protein [Homo sapiens] >gi 806806 cell surface glycoprotein [Homo sapiens] >gi 1832296 metastasis suppressor [Homo sapiens] >pir 38942 A46493 metastasis suppressor KAI1 - human >sp P27701 CD82_HUMAN CD82 ANTIGEN (INDUCIBLE MEMBRANE PRO	gi 35833	1	594	65	67	HUVCRA1
83	720903	cDNA isolated for this protein using a monoclonal antibody directed against the p27k prosomal protein [Homo sapiens] Length = 266	gn PID e103161	108	614	93	95	HFV1H35

84	721348	G6PD (AA 1-515) [Homo sapiens] >sp P11413 G6PD_HUMAN GLUCOSE-6-PHOSPHATE 1-DEHYDROGENASE (EC 1.1.1.49) (G6PD). {SUB 2-515} >gi 439445 glucose-6-phosphate dehydrogenase [Didelphis virginiana] {SUB 258-288} >sp O46666 O46666 GLUCOSE-6-PHOSPHATE DEHYDROGENAS	gi 31543	545	2065	93	93	HSHBL14
85	721562	pescadillo [Homo sapiens] >sp O00541 O00541 PESCADILLO. Length = 588	gi 2194203	32	811	99	99	HCFCK84
86	722775			409	1680			HCHAD52
87	724463			126	335			HOFMP50
88	727501	SWI/SNF complex 170 KDa subunit [Homo sapiens] >sp Q92923 Q92923 SWI/SNF COMPLEX 170 KDA SUBUNIT. Length = 1213	gi 1549241	1	1302	97	97	HL YBV46
89	728418	GTP binding protein [Mus musculus] >pir A39611 A39611 probable GTP-binding protein - mouse >sp P23249 MV10_MOUSE PROTEIN MOV-10. >gi 433685 gb 110/Mov 10 locus gene product [Mus musculus] {SUB 1-45} Length = 1004	gi 53169	3	911	93	96	HSSPE09
90	728920	adipophilin [Homo sapiens] >sp Q99541 Q99541 ADIPOPHILIN (FRAGMENT). Length = 437	gm P1D1e292752	2	751	89	89	HILDRQ71
91	732958			3	296			HPTYA52

92	733134	NF45 protein [Homo sapiens] >pir A54857 A54857 transcription factor NF-AT 45K chain - human >sp Q12905 Q12905 NF45 PROTEIN. Length = 406	gj 532313	84	1259	100	100	HHBHP80
93	734099			150	365			HBGDI44
94	734599			163	705			H6EED05
95	736019	ribosomal protein L11 [Homo sapiens] >gj 57678 ribosomal protein L11 [Rattus rattus] >pir SI17351 RSRT11 ribosomal protein L11 precursor - rat >sp G3115334 G3115334 RIBOSOMAL PROTEIN L11. >sp D1026769 D1026769 RIBOSOMAL PROTEIN L11 (FRAGMENT). {SUB 17-52}	gj 3115334	3	608	100	100	HSEBB02
96	738268			45	233			HE2OC41
97	738911	(AF069291) hT41 [Homo sapiens] >sp G3687829 G3687829 HT41. Length = 505	gj 3687829	3	656	40	62	HCHCI12
98	739226			3	125			HADFY59
99	739527			3	752			HACCL62
100	740710	acyl-CoA synthetase-like protein [Homo sapiens] Length = 670	gn PID e3212 96	8	307	96	100	HPMFQ72

101	742980	serine-threonine specific protein phosphatase [Homo sapiens] >sp E1334695 E1334695 SERINE-THREONINE SPECIFIC PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 317	gnl PID e1334695	3	182	81	86	HSKCE51
102	744331	ZINC FINGER PROTEIN {N-TERMINAL}. Length = 77	sp G632682 G632682	432	791	62	80	HCHAH75
103	744751	collagen alpha 3(VI) chain precursor - human Length = 2970	pir S13679 C GHU3A	902	1189	100	100	HUFFV63
104	745750			349	714			HCEHX66
105	746285			2016	2297			HNTNQ78
106	746416	(AB013357) 49 kDa zinc finger protein [Mus musculus] Length = 460	gnl PID d1038083	113	391	97	97	HOFMO90
107	747851	(AF035387) C7-1 protein [Rattus norvegicus] >sp O54715 O54715 C7-1 PROTEIN. Length = 463	gil 2655418	3	974	78	80	HSSIG21
108	750632			252	449			HOGBF68
109	751315			423	608			HLTGN10
110	754009			408	773			HE8PN81
111	754634			525	1070			HUSGH70
112	756637	(AF044127) peroxisomal short-chain alcohol dehydrogenase [Homo sapiens] >sp G4105190 G4105190 PEROXISOMAL SHORT-CHAIN ALCOHOL DEHYDROGENASE. Length = 260	gil 4105190	38	586	89	91	HMWY27

113	756833		1	387			HCEDP17
114	756878		127	399			IIIBDE92
115	757332	cytokeratin 8 [Homo sapiens] >gil553163 keratin 8 [Homo sapiens] {SUB 1-231} Length = 482	35	235	96	100	HOFM152
116	760835	Pectinase gene transcriptional regulator. [Escherichia coli] >gnlPID1015936 Pectinase gene transcriptional regulator. [Escherichia coli] >gil1787806 (AE000250) putative transcriptional regulator LYSR- type [Escherichia coli] >pir/A64907/A64907 hypothesi	3	434	100	100	HE9BW44
117	761760	F45G2.10 [Caenorhabditis elegans] >sp O62252 O62252 F45G2.10 PROTEIN. Length = 160	3	527	61	81	HMWIF41
118	762520	B-myb protein (AA 1-700) [Homo sapiens] >pir S01991 S01991 transforming protein B-myb - human >sp P10244 MYBB_HUMAN MYB- RELATED PROTEIN B (B-MYB). Length = 700	77	520	100	100	HBJJB76
119	764461		2	211			HOFMH95
120	764517	phosphomevalonate kinase [Homo sapiens] >sp Q15126 PMKA_HUMAN PHOSPHOMEVALONATE KINASE (EC 2.7.4.2) (PMKASE). {SUB 2-192} >gil3445542 (AF026069) phosphomevalonate kinase [Homo sapiens] {SUB 33-192} Length = 192	260	877	100	100	HCGAA73

121	765132	clk1; putative [Homo sapiens] >pir S53641 S53641 protein kinase clk1 (EC 2.7.1.-) - human >sp P49759 CLK1_HUMAN PROTEIN KINASE CLK1 (EC 2.7.1.-) (CLK). Length = 484	gi 632964	1202	2251	99	99	HE9QA05
122	765667	(AF043250) mitochondrial outer membrane protein [Homo sapiens] >gi 3941347 (AF043253) mitochondrial outer membrane protein [Homo sapiens] >gi 4105703 (AF050154) D19S1177E [Homo sapiens] >sp G3941342 G3941342 MITOCHONDRIAL OUTER MEMBRANE PROTEIN. >sp G3941	gi 3941342	144	1115	91	91	HCHOB54
123	767113	putative progesterone binding protein [Homo sapiens] >sp O00264 Q00264 PUTATIVE PROGESTERONE BINDING PROTEIN. Length = 195	gnl PID e3141 74	66	677	93	93	HNTMW26
124	767204	cytochrome P45011C4 [Oryctolagus cuniculus] >pir S20227 S20227 cytochrome P450 2C4 - rabbit (fragment) >sp Q29507 Q29507 CYTOCHROME P450 (EC 1.14.14.1) (FRAGMENT). Length = 145	gi 164933	3	581	43	61	HCHAN75
125	767400			2	1057			HSYBI74

126	767962	proteasome subunit C3 [Homo sapiens] >pir S15970 SNHUC3 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C3 - human >sp P25787 PRC3_HUMAN PROTEASOME COMPONENT C3 (EC 3.4.99.46) (MACROPAIN SUBUNIT C3) (MULTICATALYTIC ENDOPEPTIDASE COMPLEX SUBUNIT (AB002086) p47 [Rattus norvegicus] >gnl P1D e294068 XY40 protein [Rattus norvegicus] >sp O35987 O35987 P47, COMPLETE CDS. Length = 370 adenine phosphoribosyltransferase [Homo sapiens] >gi 28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir S06232 RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp P07741 APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7)	gnl P1D d100 1115	3	722	100	100	HABAF63
127	768040	(AB002086) p47 [Rattus norvegicus] >gnl P1D e294068 XY40 protein [Rattus norvegicus] >sp O35987 O35987 P47, COMPLETE CDS. Length = 370 adenine phosphoribosyltransferase [Homo sapiens] >gi 28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir S06232 RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp P07741 APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7)	gnl P1D d102 2509	119	661	84	89	HSRDI53
128	769956	adenine phosphoribosyltransferase [Homo sapiens] >gi 28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir S06232 RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp P07741 APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7)	gi 178867	2	592	100	100	HUFFC71
129	770133	ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7)		958	1236			HUSAX93
130	770289	ALDH7 [Homo sapiens] >pir 138669 138669 ALDH7 - human >sp P43353 DHA7_HUMAN ALDEHYDE DEHYDROGENASE 7 (EC 1.2.1.5). >sp G601780 G601780 ALDH7. Length = 468	gi 601780	194	340	65	69	HCHAO38

131	771964	(AD000092) human RAD23A homolog [Homo sapiens] >gnl PID d1005299 HHR23A protein [Homo sapiens] >pir S44443 S44443 RAD23 protein homolog2 - human Length = 363 B-myb protein (AA 1-700) [Homo sapiens] >pir S01991 S01991 transforming protein B-myb - human >sp P10244 MYBB_HUMAN MYB- RELATED PROTEIN B (B-MYB). Length = 700 zinc finger protein [Homo sapiens] >pir I38620 I38620 zinc finger protein ZNF155 - human (fragment) Length = 139	gil1905912	29	1165	76	76	HAMGD77
132	772582	novel serine protease, PRSS11 [Homo sapiens] >gnl PID d1014012 serin protease with IGF-binding motif [Homo sapiens] >sp Q92743 Q92743 NOVEL SERINE PROTEASE. Length = 480 protein of unknown function [Homo sapiens] >pir C35826 C35826 hypothetical protein A, 13K - human >sp Q00994 HG74_HUMAN OVARIAN GRANULOSA CELL 13.0 KD PROTEIN HGR74. Length = 111	gil29472	150	974	99	99	HYAAO51
133	773387	novel serine protease, PRSS11 [Homo sapiens] >gnl PID d1014012 serin protease with IGF-binding motif [Homo sapiens] >sp Q92743 Q92743 NOVEL SERINE PROTEASE. Length = 480 protein of unknown function [Homo sapiens] >pir C35826 C35826 hypothetical protein A, 13K - human >sp Q00994 HG74_HUMAN OVARIAN GRANULOSA CELL 13.0 KD PROTEIN HGR74. Length = 111	gil495576	152	634	64	46	HAJBC78
134	773827	novel serine protease, PRSS11 [Homo sapiens] >gnl PID d1014012 serin protease with IGF-binding motif [Homo sapiens] >sp Q92743 Q92743 NOVEL SERINE PROTEASE. Length = 480 protein of unknown function [Homo sapiens] >pir C35826 C35826 hypothetical protein A, 13K - human >sp Q00994 HG74_HUMAN OVARIAN GRANULOSA CELL 13.0 KD PROTEIN HGR74. Length = 111	gnl PID e2751 86	3	1217	100	100	HKADP15
135	774108	novel serine protease, PRSS11 [Homo sapiens] >gnl PID d1014012 serin protease with IGF-binding motif [Homo sapiens] >sp Q92743 Q92743 NOVEL SERINE PROTEASE. Length = 480 protein of unknown function [Homo sapiens] >pir C35826 C35826 hypothetical protein A, 13K - human >sp Q00994 HG74_HUMAN OVARIAN GRANULOSA CELL 13.0 KD PROTEIN HGR74. Length = 111	gil189379	303	623	75	75	HEGAC01



136	774636	glutathione transferase [Homo sapiens] >pir A39375 A39375 glutathione transferase (EC 2.5.1.18) class mu, GSTM2 - human >sp P28161 ICTM2_HUMAN GLUTATHIONE S-TRANSFERASE MU 2 (EC 2.5.1.18) (GSTM2-2) (CLASS-MU). {SUB 2-218} >gnl PID e33921 glutathione transf	gij 183301	61	747	98	98	HISDV78
137	775339	SWI/SNF complex 60 KDa subunit [Homo sapiens] >sp Q92924 Q92924 SWI/SNF COMPLEX 60 KDA SUBUNIT. Length = 435	gij 1549243	3	320	98	100	HISGB35
138	775582			448	705			HEPNB30
139	775779	(AJ000332) Glucosidase II [Homo sapiens] >sp Q14697 Q14697 GLUCOSIDASE II PRECURSOR (K1AA0088). >gnl PID d1008224 The hla1225 gene product is related to human alpha-glucosidase. [Homo sapiens] {SUB 2-944} Length = 944	gnl PID e328143	1	1695	98	98	HLWAS86
140	777809	cysteine-rich protein 2 [Homo sapiens] >gnl PID d1008288 ESP1/CRP2 [Homo sapiens] >pir G02090 G02090 cysteine-rich protein 2 - human >sp P52943 CRP2_HUMAN CYSTEINE-RICH PROTEIN 2 (CRP2) (ESPI PROTEIN). Length = 208	gij 1399028	202	681	99	100	HSPMB57
141	778927	valyl-tRNA synthetase [Homo sapiens] >pir S17675 S17675 valine--tRNA ligase (EC 6.1.1.9) - human Length = 1265	gij 31545	1843	3282	88	88	HMVVBW39

142	779262		1	288		HTENK29
143	779392		2	181		HE2FO87
144	780149	proteasome activator hPA28 suunit beta [Homo sapiens] >pir I53518 I53518 proteasome activator hPA28 suunit beta - human >sp Q15129 Q15129 PROTEASOME ACTIVATOR HPA28 SUUNIT BETA. >sp G693763 G693763 PA28=REGULATORS OF THE 20 S PROTEASOME {PEPTIDE 15}. {SUB	233	955	93	HSPMF83
145	780583		8	607		HHIEW04
146	780960		232	576		HOEBN65
147	781469	radixin [Homo sapiens] >pir A46127 A46127 radixin - human Length = 583	1	303	100	HNTRA25
148	781556		116	190		HOSAW82
149	781771		1	822		HE6EO05
150	782033	histone H2A [Gallus gallus] Length = 129	146	544	98	HULCC66
151	782105		606	1064	100	HKAKV16

152	782122	high density lipoprotein binding protein [Homo sapiens] >pir A44125 A44125 high density lipoprotein-binding protein, 110K - human >sp Q00341 HBP_HUMAN HIGH DENSITY LIPOPROTEIN BINDING PROTEIN (HDL-BINDING PROTEIN). >sp G1478463 G1478463 VIGILIN=KH PROTEIN	gij183892	3	983	95	95	HSRAB32
153	783135	zinc finger protein [Homo sapiens] >sp O00488 O00488 ZINC FINGER PROTEIN. Length = 116	gn P D d 102 1201	3	500	97	99	HCHCB61
154	783245			3	341			H'ISFV77
155	783247			95	391			HIBGMD18
156	783413	D9 splice variant 3 [Mus musculus] >sp O08695 O08695 D9 SPLICE VARIANT 3. Length = 169	gij2071991	1	591	80	88	HIEBFR23
157	784407			45	185			HFKAA09
158	784548	nuclear RNA helicase (DEAD family) [Homo sapiens] >pir I37201 I37201 nuclear RNA helicase (DEAD family) BAT1 - human >sp Q13838 HE47_HUMAN PROBABLE ATP-DEPENDENT RNA HELICASE P47. >gij2739119 (AF029061) BAT1 [Homo sapiens] {SUB 145-428} >gij971677 express	gij587146	676	1020	90	92	HSRFZ85

159	785075	KIAA0100 is a human counterpart of mouse e1 gene. [Homo sapiens] >sp Q14667 Q14667 KIAA0100 (HUMAN COUNTERPART OF MOUSE E1 GENE). Length = 2092	gnl PI D d 100 8477	72	1109	93	93	HDPFX40
160	785677	(AC004084) similar to DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE; 98% similar to P5243 (PID:gl710661) [Homo sapiens] >sp O43375 O43375 SIMILAR TO DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE (FRAGMENT). Length = 105	gi 2822158	1	273	95	100	HBSAJ50
161	786238			2	994			HOVCA75
162	786389			3	1124			ILJDU61
163	786929	(A1224442) methyltransferase [Homo sapiens] >sp O43709 O43709 METHYLTRANSFERASE. Length = 220 PIPPin protein [Rattus norvegicus] >pir JC4588 JC4588 RNA-binding protein PIPPin - rat >sp Q63430 Q63430 PIPPIN PROTEIN. Length = 154	gnl PI D e 1253 426	123	404	86	95	HOINNV27
164	786932		gi 1050754	2	490	76	87	HUSYH27
165	787078	HER2 receptor [Homo sapiens] >gi 553282 c-erb-2 protein [Homo sapiens] {SUB 737-1031} >gi 553332 HER-2/neu [Homo sapiens] {SUB 1-191} >gi 183989 HER2 receptor (AA at 3) [Homo sapiens] {SUB 740-910} >gi 182169 c-erb B2/neu protein [Homo sapiens] {SUB 1081}-	gi 306840	236	1114	79	79	HCHND12

166	787139			230	625		HBCBA06
167	787283			3	656		HFOYO96
168	788761	MAL3P6.24 [Plasmodium falciparum] >sp O77371 O77371.MAL3P6.24 PROTEIN. Length = 1017	gn P D e 331 909	2	700	36	HTXFK57
169	788988	(AF023611) Dim 1p homolog [Homo sapiens] >sp O14834 O14834.DIM1P HOMOLOG. Length = 142	gi 2565275	70	417	98	HUSGH90
170	789092			2	400		H6EBE80
171	789298	(AF044311) gamma-synuclein [Homo sapiens] >gi 3642775 (AF017256) persyn [Homo sapiens] >gi 3642903 (AF037207) persyn [Homo sapiens] >sp O76070 O76070.PERSYN. Length = 127	gi 3347842	1	489	82	HTSFM20
172	789299			205	381		HBGDD91
173	789718			233	580		HIBGIBT30
174	789957	beta-hexosaminidase alpha chain [Homo sapiens] >pir A23561 AOHUBA beta-N- acetylhexosaminidase (EC 3.2.1.52) alpha chain precursor - human >sp P06865 HEXA_HUMAN BETA- HEXOSAMINIDASE ALPHA CHAIN PRECURSOR (EC 3.2.1.52) (N-ACETYL- BETA-GLUCOSAMINIDASE) (BETA-	gi 179458	750	1619	99	HISEM44

175	789977	arginyl-tRNA synthetase, ArgRS [human, ataxia-telangiectasia patients, EBV-lymphoblastoid cells, Peptide, 659 aa] [Homo sapiens] >pir JC4365 JC4365 arginine--tRNA ligase (EC 6.1.1.19) - human Length = 659	bbs 173838	25	2019	94	95	HMEIU30
176	790285	HCG V [Homo sapiens] >sp O60927 O60927 HCG V. Length = 126	gi 3176438	44	391	85	85	HDPCH88
177	790509	human elongation factor-1-delta [Homo sapiens] >pir S34626 S34626 translation elongation factor eEF-1 delta chain - human >sp P29692 EF1D_HUMAN ELONGATION FACTOR 1-DELTA (EF-1-DELTA). Length = 281	gi 38522	227	1108	63	64	HPMGB64
178	790775			950	1351			HJAAO21
179	790888	(AF036956) neuroblastoma apoptosis-related RNA binding protein [Homo sapiens] >sp G4104559 G4104559 NEUROBLASTOMA APOPTOSIS-RELATED RNA BINDING PROTEIN. Length = 490	gi 4104559	2	274	100	100	HE8QE19
180	791506			2	205			HO1MB93
181	791649			3	359			HBGBH10
182	791802			165	695			HWLRH03

183	792002	ADP-ribosylation factor [Homo sapiens] >gi 2088529 ADP-ribosylation factor 5 [Homo sapiens] >gi 438870 ADP- ribosylation factor 5 [Rattus norvegicus] >gn P1D1014187 ARF5 [Mus musculus] >pir A23741 A23741 ADP-ribosylation factor 5 - human >pir C4949 C4	gi 178987	2	655	100	100	HHENT53
184	792291	see GenBank Accession Number U01184 for cDNA; similar to Drosophila melanogaster fil1 in GenBank Accession Number U01182 and Caenorhabditis elegans fil1 homolog in GenBank Accession Number U01183 [Homo sapiens] >sp Q13045 Q13045 FLIGHTLESS-1 PROTEIN HOMOL	gi 2138290	843	3329	96	96	HDPIT69
185	792371			3	665			HUSJW77
186	792660	(AF044773) breakpoint cluster region protein 1 [Homo sapiens] >sp O60558 O60558 BREAKPOINT CLUSTER REGION PROTEIN 1. Length = 138	gi 3002951	116	406	100	100	HCHMC26
187	792782			41	838			HTXJB38
188	792890	(AF001846) lymphoid phosphatase LyP1 [Homo sapiens] >sp G4100632 G4100632 LYMPHOID PHOSPHATASE LYPI. Length = 808	gi 4100632	2	994	90	90	HHESJ29
189	792931			1	576			HEGAW71

190	792943	myosin heavy chain kinase B [Dictyostelium discoideum] >sp P90648 KMHIB_DICDI MYOSIN HEAVY CHAIN KINASE B (EC 2.7.1.129) (MHCK B). Length = 732	gi 1903458	3	1247	43	68	IIDPRZ79
191	793104			107	250			HKGAJ80
192	793445	desmoyokin - human (fragments) >sp Q09666 AHNK_HUMAN NEUROBLAST DIFFERENTIATION ASSOCIATED PROTEIN AHNK (DESMOYOKIN) (FRAGMENTS). >gi 178281 AHNAK_nucleoprotein [Homo sapiens] {SUB 1-1683} >gi 897824 AHNAK gene product [Homo sapiens] {SUB 1684-2960} Leng	pir A45259 A 45259	1	723	92	92	HDTEJ86
193	793446			25	255			HLIBGY94
194	793639	(AF044959) NADH:ubiquinone oxidoreductase NDUFS6 subunit [Homo sapiens] >sp O75380 NUMM_HUMAN NADH-UBIQUINONE OXIDOREDUCTASE 13 KD-A SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3). (COMPLEX 1-13KD-A) (CI-13KD-A). Length = 124	gi 3348137	1	411	100	100	HLJB172
195	794213	100 kDa protein [Rattus norvegicus] >pir S22659 S22659 hypothetical protein, 100K - rat >sp Q62671 100K_RAT 100 KD PROTEIN (EC 6.3.2.-). Length = 889	gi 55535	326	691	93	95	HLWCN67
196	795858			1020	1205			HLVDY53



197	795955	c-myc binding protein [Homo sapiens] >sp Q99471 MM1_HUMAN C-MYC BINDING PROTEIN MM-1. >sp D1014706 D1014706 C-MYC BINDING PROTEIN. Length = 167 ribosomal protein L7a large subunit [Homo sapiens] >gi 34203 L7a protein [Homo sapiens] >gi 35512 PLA-X polypeptide [Homo sapiens] >gi 36647 ribosomal protein L7a [Homo sapiens] >gi 56956 ribosomal protein L7a (AA 1-266) [Rattus rattus] >pir S19717 R5HU7A	gn P D d 101 4706	31	507	100	100	HUSXX36
198	796359	ribosomal protein L7a large subunit [Homo sapiens] >gi 34203 L7a protein [Homo sapiens] >gi 35512 PLA-X polypeptide [Homo sapiens] >gi 36647 ribosomal protein L7a [Homo sapiens] >gi 56956 ribosomal protein L7a (AA 1-266) [Rattus rattus] >pir S19717 R5HU7A	gi 337495	19	297	100	100	HOFNW79
199	796555	DJ366N23.3 (KIAA0173 AND TUBULIN- TYROSINE LIGASE LIKE) (FRAGMENT). Length = 278 PEG1/MEST [Homo sapiens] >sp O15007 O15007 PEG1/MEST GENE MRNA. Length = 335 (AF022229) translation initiation factor 6 [Homo sapiens] >gn P D e 304603 b4 integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gc1 homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT	sp O75653 O7 5653	1	1086	44	62	HLWEW04
200	796675	PEG1/MEST [Homo sapiens] >sp O15007 O15007 PEG1/MEST GENE MRNA. Length = 335 (AF022229) translation initiation factor 6 [Homo sapiens] >gn P D e 304603 b4 integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gc1 homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT	gn P D e 3070 37	44	1027	100	100	HSICR25
201	796743	(AF022229) translation initiation factor 6 [Homo sapiens] >gn P D e 304603 b4 integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gc1 homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT	gi 2809383	30	842	100	100	H6EDU12
202	796792			198	461			HDTI172
203	799668			166	303			HODBC01
204	799669			2	310			HOGAV29

205	799673		2	310		HOFMN53
206	799674		130	1044		HCHM160
207	799678	ribosomal protein L18a [Homo sapiens] >gi 3702270 (AC005796) ribosomal protein L18a [Homo sapiens] >gn P1D1d1029536 (AB007175) ribosomal protein L18a [Homo sapiens] {SUB 111-176} Length = 176	40	345	98	HOFNL25
208	799728		3	179		HBBG75
209	799748		1	660		IIC11MQ24
210	799760	o361 [Escherichia coli] >gi 1790125 (AE000446) orf, hypothetical protein [Escherichia coli] >pir C65171 C65171 hypothetical 41.0 kD protein in ibpA-gyrB intergenic region - Escherichia coli (strain K-12) Length = 361	1	357	99	IIBGBF66
211	799805		2	118		HBGDA22
212	800296	CDC37 homolog [Homo sapiens] >gi 1375485 CDC37 homolog [Homo sapiens] >pir G02313 G02313 CDC37 homolog - human >sp Q16543 Q16543 CDC37 HOMOLOG. Length = 378	2	802	89	HDABE68

213	800327	ADP-ribosylation factor-like protein 2 [Homo sapiens] >pir A48259 A48259 ADP- ribosylation-factor-like 2 - human >sp P36404 ARL2_HUMAN ADP- RIBOSYLATION_FACTOR-LIKE PROTEIN 2. >sp G425655 G425655 ARL2=ADP-RIBOSYLATION FACTOR HOMOLOG. Length = 184	gi 3009501	25	645	99	99	HCHPG41
214	800816			115	351			HODCV09
215	800835	(AF071538) Ets transcription factor PDEF [Homo sapiens] >sp G4007418 G4007418 ETS TRANSCRIPTION FACTOR PDEF. Length = 335	gi 4007418	3	881	96	96	HETJP29
216	805429	RanGAP1 [Homo sapiens] >pir JC5300 JC5300 Ran GTPase activator 1 - human Length = 587	gi 575268	3	683	90	90	HKAIS06
217	805458	(AF044221) HCG-1 protein [Homo sapiens] >sp G4105252 G4105252 HCG-1 PROTEIN. Length = 117	gi 4105252	745	1122	100	100	HDQEV55
218	805478			60	644			HDQGR35
219	805805	19 kDa subunit of NADH:ubiquinone oxidoreductase complex (complex I) [Bos taurus] >pir S16208 S16208 NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) 19K chain - bovine >sp P42029 NUPM_BOVIN NADH- UBIQUINONE OXIDOREDUCTASE 19 KD SUBUNIT (EC 1.6.5.3) (EC 1.6.99	gi 599681	2	478	87	90	HOFMH12
220	806486			3	62			HFXJC33



## interacting prote

229	815853	calcyphosine [Homo sapiens] >gi 3075376 (AC004602) CAYP_HUMAN; RD25 [Homo sapiens] >sp Q13938 CAYP_HUMAN CALCYPHOSINE. Length = 189	gn P D e2458 72	8	667	100	100	HLHAY85
230	815999	S100 calcium-binding protein A13 (S100A13) [Homo sapiens] >pir JC5064 JC5064 S-100 calcium-binding protein A13 - human Length = 98	gn P D e2682 53	68	421	42	70	HKABX07
231	823427			1	927			HTLGL50
232	823704	(AC004770) BC269730_2 [Homo sapiens] >sp O60427 O60427 BC269730_2. Length = 444	gi 3169158	3	860	67	80	HDABC49
233	824798			307	858			HDQKG75
234	825018			2	1924			HETIS29
235	825076	Whole ORF continues from bp19 (right after 'tag') to bp1596 ('tag'); similar to chinese hamster phosphatidylserine synthase. [Homo sapiens] Length = 473	gn P D d100 4031	2	1549	92	92	HE9PJ48

236	825787	EXT2 [Homo sapiens] >gi 1621113 hereditary multiple exostoses gene 2 protein [Homo sapiens] >gi 1519605 multiple exostosis 2 [Homo sapiens] >sp Q93063 EXT2_HUMAN EXOSTOSIN-2 (PUTATIVE TUMOUR SUPPRESSOR PROTEIN EXT2) (MULTIPLE EXOSTOSES PROTEIN 2). Length BETA CRYSTALLIN S (GAMMA CRYSTALLIN S). >gi 557548 crystallin [Homo sapiens] {SUB 19-106} Length = 177 neural specific protein CRMP-2 [Bos taurus] >sp O02675 DPY2_BOVIN DIHYDROXYRIMIDINASE RELATED PROTEIN-2 (DRP-2) (NEURAL SPECIFIC PROTEIN NSP60). Length = 572 (AF027954) Bcl-2-related ovarian killer protein [Rattus norvegicus] >gi 2689660 (AF027707) apoptosis activator Mtd [Mus musculus] >sp O35425 O35425 BCL-2- RELATED OVARIAN KILLER PROTEIN. Length = 213	gi 1518042	305	2293	100	100	HEONV84
237	826116		sp P22914 CR BS_HUMAN	392	682	86	87	HAAJAE27
238	826147		gi 1916227	3	503	98	98	HCEPT06
239	827020		gi 2645560	12	539	95	97	HHFHE17
240	827586	calmodulin [Plasmodium falciparum] >gi 160128 calmodulin [Plasmodium falciparum] >pir B45594 MCZQF calmodulin - Plasmodium falciparum >sp P24044 CALM_PLAFA CALMODULIN. Length = 149	gi 385234	85	495	49	76	HCHMW40

241	827732	alternate name ygiG; ORF_f123 [Escherichia coli] >gij1789438 (AE000387) putative kinase [Escherichia coli] >pir H65093 H65093 ygiG protein - Escherichia coli (strain K-12) >sp P31055 FOLB_ECOLI PROBABLE DIHYDRONEOPTERIN ALDOLASE (EC 4.1.2.25) (DHNA). {SUB	gij1882580	181	282	91	95	HBCDE81
242	827735			541	708			IHHEDU22
243	827740			716	838			HBNAP17
244	827808			86	1657			HMEELR44
245	828251	(AB016869) p70 ribosomal S6 kinase beta [Homo sapiens] >sp D1035383 D1035383 P70 RIBOSOMAL S6 KINASE BETA. Length = 495	gnl PID d103 5383	134	949	91	91	INGO1.64
246	828357			1	768			HK1YP61
247	828449			1	723			HXCZ22
248	828612	syntaxin 5 [Homo sapiens] >pir G01817 G01817 syntaxin 5 - human Length = 301	gij1886071	68	460	100	100	IINHMY58
249	828647	laminin beta 2 chain [Homo sapiens] >sp P55268 LMB2_HUMAN LAMININ BETA-2 CHAIN PRECURSOR (S- LAMININ). Length = 1798	gnl PID e2132 86	299	2254	85	85	HRABB47

250	828698	galactokinase [Homo sapiens] >gi 1929895 galactokinase [Homo sapiens] >sp P51570 GAL1_HUMAN GALACTOKINASE 1 (EC 2.7.1.6). >gi 3603423 (AF084935) galactokinase [Homo sapiens] {SUB 1-264} Length = 392	gi 1002507	3	1220	83	83	HKG AU37
251	828962	secretory protein [Homo sapiens] >gi 940946 intestinal trefoil factor [Homo sapiens] >pir A48284 A48284 intestinal trefoil factor 3 precursor - human >sp Q07654 ITF_HUMAN INTESTINAL TREFOIL FACTOR PRECURSOR (HP1.B). Length = 80 unnamed protein product [unidentified] >gi 189500 p62 [Homo sapiens] >pir A38219 A38219 GAP-associated tyrosine phosphoprotein p62 - human >sp Q07666 Q07666 GAP-ASSOCIATED TYROSINE PHOSPHOPROTEIN P62. >gnl PID e1259626 unnamed protein product [unidentified]	gi 402483	2	259	78	78	HCHMR32
252	828982	unnamed protein product [unidentified] >gi 189500 p62 [Homo sapiens] >pir A38219 A38219 GAP-associated tyrosine phosphoprotein p62 - human >sp Q07666 Q07666 GAP-ASSOCIATED TYROSINE PHOSPHOPROTEIN P62. >gnl PID e1259626 unnamed protein product [unidentified]	gnl PID e1259626	1	1176	85	85	HE9PC52
253	829282	(AF109906) G9A [Mus musculus] >sp G3986768 G3986768 G9A. Length = 1000	gi 3986768	26	862	97	98	HCHOB95 HWGAA79 HCHMB33 HMWBV67
254	829368		gi 3986768	279	512			
255	829751		gi 3986768	2	418			
256	829773		gi 3986768	26	862	97	98	



257	829934	precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir A35954 A35954 endoplasmin precursor - human >sp P14625 ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 K D GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803 dynamitin [Homo sapiens] >sp Q13561 DYNC_HUMAN DYNACTIN, 50 K D ISOFORM (50 K D DYNEIN-ASSOCIATED POLYPEPTIDE) (DYNAMITIN). Length = 406	gil37261	1142	2356	94	94	HFIIJ68
258	829942		gil1255188	15	1409	85	85	HUFBF69
259	829951			119	262			HIBGBA32
260	830173	death associated protein 5 [Homo sapiens] >sp O60877 O60877 DEATH ASSOCIATED PROTEIN 5. Length = 907	gnl PID e1298 888	51	2870	90	90	HETIX39
261	830200			3	638			HBCMF83
262	830365	mevalonate pyrophosphate decarboxylase [Homo sapiens] >sp P53602 ER19_HUMAN DIPHOSPHOMEVALONATE DECARBOXYLASE (EC 4.1.1.33) (MEVALONATE PYROPHOSPHATE DECARBOXYLASE). Length = 400	gil1235682	56	1291	95	95	HUSIG21
263	830456			215	397			HICFBN01

264	830549	guanine nucleotide-binding regulatory protein-beta-2 subunit [Homo sapiens] >gi 339935 transducin beta-2 subunit [Homo sapiens] >gi 3135310 (AF053356) GNB2 [Homo sapiens] >pir B26617 RGHUB2 GTP-binding regulatory protein beta-2 chain - human >sp P11016 GB	gi 386751	1	729	100	100	100	HTLDM12
265	830602			24	461				HTLDM82
266	830610	zyxin [Homo sapiens] >gn P1D e223417 zyxin [Homo sapiens] >pir G02845 G02845 zyxin - human Length = 572	gn P1D e2182 60	956	1855	94	94	94	HTLDM35
267	830644	(AF104260) hiwi [Homo sapiens] >sp G4038413 G4038413 HIW1 (FRAGMENT). Length = 523	gi 4038413	2	391	99	99	99	HTLDM95
268	830707			3	623				HETCJ14
269	830709			2	304				HSSGN20
270	830733			540	725				HSNAD86
271	830768	carboxylesterase hCE-2 [Homo sapiens] >sp Q16859 Q16859 CARBOXYLESTERASE (EC 3.1.1.1) (AL1-ESTERASE) (B-ESTERASE) (MONOBUTYRASE) (COCAINE ESTERASE) (PROCAINE ESTERASE) (METHYLBUTYRASE). Length = 550	gi 407780	623	2269	99	99	99	HTLDM44
272	830855			1	465				HUPCE06

273	830949		2457	2903	HCE5J35
274	830965		139	792	II0IIC'A01
275	830973		354	557	HR0DL42
276	830979	THIOREDOXIN REDUCTASE 2. Length = 526	753	1454	HOGCC93
277	830989	La protein [Homo sapiens] >gi 36415 ribonucleoprotein SS-B/La (AA 1-408) [Homo sapiens] >pir A31888 A31888 ribonucleoprotein La - human >sp P05455 LA_HUMAN LUPUS LA PROTEIN (SJOEGREN SYNDROME TYPE B ANTIGEN (SS-B)) (LA RIBONUCLEOPROTEIN) (LA AUTOANTIGEN).	3	1382	HDQF'Z49
278	831134		2	241	HBXEB46
279	831200		3	773	HADXB20
280	831260		892	1095	HLWBR58
281	831531	transcription factor [Homo sapiens] >gi 37058 IIB protein [Homo sapiens] >pir S17654 TWHU2B transcription initiation factor IIB - human >bbs 112738 S300-II, TFIIB=transcription factor [human, Peptide Partial, 311 aa] [Homo sapiens] {SUB 6-316} Length = 31	93	1172	HHPGX85
282	831665		2	1093	HSKDH81

283	831724			1	468				HFEBQ94
284	831884	(AF034800) liprin-alpha3 [Homo sapiens] >sp G3309535 G3309535 LIPRIN- ALPHA3 (FRAGMENT). Length = 443	gi 3309535	20	469	90	90		HD TGO74
285	831897	laminin B1 [Homo sapiens] >gi 186876 laminin B1 [Homo sapiens] >gi 186913 laminin B1 [Homo sapiens] >pir S13547 MMHUB1 laminin chain B1 precursor - human >sp P07942 LMB1_HUMAN LAMININ BETA-1 CHAIN PRECURSOR (LAMININ B1 CHAIN). Length = 1786	gi 186837	1	1581	92	92		HSK H V84
286	831922			499	684				HDQIB68
287	831963			188	319				HDPGS84
288	832074	gluconate kinase [Escherichia coli] >gi 1790719 (AE000497) gluconate kinase, thermosensitive glucokinase [Escherichia coli] >pir S56494 S56494 gluconokinase (EC 2.7.1.12) gntV - Escherichia coli >sp P39208 GNTV_ECOLI THERMOSENSITIVE GLUCONOKINASE (EC 2.7.	gi 537110	1	579	42	58		HCRNT71
289	832266			71	433				HNGJU70
290	832309			1891	2226				HBJDT21
291	832342	fatty acid amide hydrolase [Homo sapiens] >sp O00519 O00519 FATTY ACID AMIDE HYDROLASE. Length = 579	gi 2149156	9	224	97	100		HBGDP82

292	832351	unknown product specific to adipose tissue [Homo sapiens] >sp Q15847 Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76	gnl PI D d100 8821	47	298	68	68	HFABE30.
293	832352	unknown product specific to adipose tissue [Homo sapiens] >sp Q15847 Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76	gnl PI D d100 8821	89	277	92	94	HOEKX93
294	832434	CksI protein homologue [Homo sapiens] >pir A36670 A36670 protein kinase cdc2 complex subunit CKS1 - human >sp P33551 CKS1_HUMAN CYCLIN- DEPENDENT KINASES REGULATORY SUBUNIT 1 (CKS-1). Length = 79	gil 29977	78	335	100	100	HFNAB43
295	832490	growth arrest and DNA-damage-inducible protein [Homo sapiens] >gil 403128 [Human gadd45 gene, complete cds.], gene product [Homo sapiens] >pir A39617 A39617 DNA-damage-inducible protein gadd45 - human >sp P24522 GA45_HUMAN GROWTH ARREST AND DNA- DAMAGE-INDU	gil 82940	220	798	98	100	HKAKL21
296	832573			30	629			HCHOY13
297	832580	pS2 protein [Homo sapiens] >gil 35707 pS2 precursor [Homo sapiens] >gnl PI D e223341 pS2 [Homo sapiens] >pir A26667 A26667 pS2 protein precursor - human >gil 82204 estrogen receptor [Homo sapiens] {SUB 2-84} Length = 84	gil 35718	45	362	100	100	H2LAR67

298	833394			274	588				HIBGMC47
299	835355	(AF060567) sushi-repeat protein [Homo sapiens] >sp O60687 O60687 SUSHI-REPEAT PROTEIN. Length = 465	gi 3108089	3	1295	99	100		HUSAU05
300	835497	(AJ006064) coronin-like protein [Rattus norvegicus] >sp O89046 O89046 CORONIN-LIKE PROTEIN. Length = 484	gnl PID e1331790	334	1584	96	99		HLDDS71
301	835728			2	871				HODAK21
302	835978			643	2019				ITFLIEB03
303	836091	PDC-E2 precursor (AA -54 to 561) [Homo sapiens] >pir S01783 XXHU dihydrolipoamide S-acetyltransferase (EC 2.3.1.12) precursor - human (fragment) >gi 345030 Human 70kd mitochondrial antigen of PBC [unidentified] {SUB 179-500} >sp G254062 G254062 PYRUVATE D	gi 35360	546	2114	99	99		I12CBW86
304	836274	Id4 [Homo sapiens] >gnl PID e266418 helix-loop-helix protein [Homo sapiens] >gnl PID e1359205 (AL022726) dJ625H18.1 (ID4 Helix-loop-helix DNA binding protein) [Homo sapiens] >gnl PID e266418 helix-loop-helix protein [Homo sapiens] >pir G01855 G01855 Id4 -	gi 881546	2	334	98	98		HCLBP52

305	836731	(AF075599) ubiquitin conjugating enzyme 12 [Homo sapiens] >gnl PI d1034111 (AB012191) Nedd8-conjugating enzyme hUbc12 [Homo sapiens] >sp O76069 O76069 UBIQUITIN-CONJUGATING ENZYME E2 (EC 6.3.2.19) (UBIQUITIN-PROTEIN LIGASE) (UBIQUITIN CARRIER PROTEIN). L	gi 3309661	2	571	100	100	HFXAZ01
306	838014	prolyl 4-hydroxylase alpha (II) subunit [Homo sapiens] >sp O15460 O15460 PROLYL 4-HYDROXYLASE ALPHA (II) SUBUNIT (II). Length = 535	gi 2439985	3	1574	99	99	HTEHY24
307	838874			271	546			HFPEZ63
308	839120	peptide transporter [Homo sapiens] >pir S13427 A41538 ATP-binding cassette transporter TAP1 - human >gi 34636 ABC-transporter [Homo sapiens] {SUB 61-808} >gi 930122 Y3 gene product [Homo sapiens] {SUB 183-612} Length = 808	gi 36061	100	2169	90	90	HNFDY03
309	839611			548	793			HAMF154
310	840138	start position 1 [Homo sapiens] >sp E1335356 E1335356 ASMTL PROTEIN. >gnl PI d1335357 start position 2 [Homo sapiens] {SUB 59-629} Length = 629	gnl PI d1335356	1	1800	92	93	HFIHW86

311	840616	Homology with Squid retinal-binding protein (PIR Acc. No. A53057) [Caenorhabditis elegans] >sp Q22467 Q22467 T13H5.2 PROTEIN. Length = 1254	gnl PIDe1349397	3	1607	73	86	HMSCY51
312	840780	unknown [Saccharomyces cerevisiae] >pir S58704 S58704 probable membrane protein YIL003w - yeast (Saccharomyces cerevisiae) >gil558401 incomplete orf, len: 160, CAl: 0.09 similar to MRP_ECOLI P21590 39.9 KD PROTEIN [Saccharomyces cerevisiae] {SUB 1-158} >g	gil763343	17	880	57	80	H6EDY61
313	840857	(AF071059) zinc finger RNA binding protein [Mus musculus] >sp O88532 O88532 ZINC FINGER RNA BINDING PROTEIN. Length = 1052 cysteine-rich intestinal protein [Homo sapiens] >pir G02666 G02666 cysteine-rich protein 1 - human Length = 77	gil3293537	459	2669	94	94	HLHDQ83
314	840862		gil1381638	36	353	100	100	HEPAP58
315	840864			407	1096			HTLHY48
316	840936	homologous to Swiss-Prot accession number P16371 [Homo sapiens] >gil3850562 (AC005944) GRG_HUMAN; ESP1 PROTEIN; AMINO ENHANCER OF SPLIT; AES-1/AES-2; gp130 associated protein GAM [Homo sapiens] >pir G01236 G01236 enhancer of split m9/m10 (groucho protein)	gil435425	3	668	79	79	HOENU32



317	840938	carbonyl reductase [Sus scrofa] >pir JN0703 JN0703 carbonyl reductase (NADPH) (EC 1.1.1.184) - pig >sp Q29529 CBR2_PIG LUNG CARBONYL REDUCTASE [NADPH] (EC 1.1.1.184) (NADPH-DEPENDENT CARBONYL REDUCTASE) (LCR). Length = 244	gnl PID d100 4479	2	745	65	76	HMCA175
318	841884			677	1324			HLQB145
319	842241	(AJ009698) embigin protein [Rattus norvegicus] >sp O88775 O88775 EMBIGIN PROTEIN PRECURSOR. Length = 328	gnl PID e1312 986	2	952	60	75	HOFMD52
320	843712			2	202			HSSGR77
321	844040	ribosomal protein L11 [Caenorhabditis elegans] >pir S27795 S27795 ribosomal protein L11 homolog - Caenorhabditis elegans Length = 195	gij I56201	75	500	42	64	HP1TGB84
322	844336	(AB009462) LDL receptor related protein 105 [Homo sapiens] >sp O75074 O75074 LDL RECEPTOR RELATED PROTEIN 105. Length = 770	gnl PID d103 3292	831	2285	68	75	HWMFE21
323	844612	collagen binding protein 2 [Homo sapiens] >pir I52968 I52968 colligin-2 - human >sp P50454 CBP2_HUMAN COLLAGEN- BINDING PROTEIN 2 PRECURSOR (COLLIGIN 2). Length = 418	gnl PID d101 2496	528	1466	96	97	HOFME75
324	844617			556	735			HMVCZ36

325	845251	LIV-1 protein [Homo sapiens] >pir G02273 G02273 LIV-1 protein - human >sp Q13433 Q13433 ESTROGEN REGULATED LIV-1 PROTEIN. Length = 752	gij1256001	23	634	49	67	HBGBB42
326	845764			2	244			HULCF61
327	846187	ATPase alpha subunit (aa 1-1023) [Homo sapiens] >gnl PID d1000505 Na,K-ATPase alpha-subunit [Homo sapiens] >pir A24414 A24414 Na+/K+-exchanging ATPase (EC 3.6.1.37) alpha-1 chain - human >sp P05023 ATNI_HUMAN SODIUM/POTASSIUM- TRANSPORTING ATPASE ALPHA-1 C	gij28927	151	2403	92	92	HDPLV27
328	HBGDH47R			167	241			IIBGID1147
329	HHENQ86R			2	112			HHENQ86
330	HBGBH23R	(AE000161) bacteriophage lambda endopeptidase homolog [Escherichia coli] >pir B64788 B64788 bacteriophage lambda endopeptidase homolog (EC 3.4.-.-) - Escherichia coli (strain K-12) >sp P75719 ENPP_ECOLI_PUTATIVE ENDOPEPTIDASE (EC 3.4.-.-). Length = 153	gij1786769	1	213	92	92	HBGBH23
331	HANGA53R	(AF013214) acidic ribosomal phosphoprotein PO [Bos taurus] Length = 302	gij2293577	76	402	80	84	HANGA53

332	HBIMC29R	(AF035959) type-2 phosphatidic acid phosphatase-gamma; phosphatidate phosphohydrolase; phospholipid phosphatase [Homo sapiens] >gil3025880 (AF056083) phosphatidic acid phosphatase type 2 [Homo sapiens] >gil2911498 (AF047760) phosphatidic acid phosphohydro (AF061340) F1 ATPase subunit 6 [Aritbeus jamaicensis] Length = 226 (AF070447) barrier-to-autointegration factor [Homo sapiens] >sp O75531 O75531 BARRIER-TO-AUTOINTEGRATION FACTOR. Length = 89	gil3123896	3	317	96	96	HBIMC29
333	HOFAB89R		gil4164480	86	268	67	82	HOFAB89
334	HAHCP93R		gil3220255	116	289	69	76	HAHCP93
335	HBGAA76R			14	232			HBGAA76
336	HBGBT12R	A (DNA packaging;641) [Bacteriophage lambda] >pir D04333 VBPAL DNA- packaging protein A - phage lambda Length = 641	gil215106	2	349	95	95	HBGBT12
337	HBGBH53R	Actin [Drosophila melanogaster] >pir S14851 S14851 actin - fruit fly (Drosophila melanogaster) >sp Q24228 Q24228 ACTIN. Length = 100	gil7550	2	445	93	97	HBGBH53

338	HTXPI29R	aldolase A (EC 4.1.3.13) [Homo sapiens] >gi 28597 aldolase A (AA 1-364) [Homo sapiens] >pir S14084 ADHUA fructose-bisphosphate aldolase (EC 4.1.2.13) A - human >sp P04075 ALFA_HUMAN FRUCTOSE-BISPHOSPHATE ALDOLASE A (EC 4.1.2.13) (MUSCLE-TYPE ALDOLASE). {S	gi 178351	1	453	86	86	HTXPI29
339	HOFMG33R	ATPase [Equus caballus] >sp P48662 ATP6_HORSE ATP SYNTHASE A CHAIN (EC 3.6.1.34) (PROTEIN 6). Length = 226	gi 577577	28	309	57	62	HOFMG33
340	HCGAC11R			1	345			HCGAC11
341	HCIAC54R			37	168			HCIAC54
342	HBGAA54R			1	282			HBGAA54
343	HAOMC34R	calpactin I heavy chain (p36) [Bos taurus] >pir A03081 LUBO36 annexin II - bovine >sp P04272 ANX2_BOVIN ANNEXIN II (LIPOCORTIN II) (CALPACTIN I HEAVY CHAIN) (CHROMOBINDIN 8) (P36) (PROTEIN I) (PLACENTAL ANTICOAGULANT PROTEIN IV) (PAP-IV). {SUB 2-339} Leng	gi 162779	2	115	73	80	HAOMC34
344	H2LAU88R	copine I [Homo sapiens] >sp Q99829 Q99829 COPINE I. Length = 537	gi 1791257	1	576	95	95	H2LAU88
345	HDPJR77R	DNA topoisomerase II [Homo sapiens] >gi 38325 DNA topoisomerase II [Homo sapiens] {SUB 448-681} Length = 1031	gi 288565	3	311	100	100	HDPJR77

346	HTT1O41R	docking protein [Homo sapiens] >pir A29440 A29440 signal recognition particle receptor - human Length = 638	gj 30866	90	404	94	95	HTT1O41
347	H2CBU29R	electron transport flavoprotein [Homo sapiens] >pir A31998 A31998 electron transfer flavoprotein alpha chain precursor - human >sp P13804 ETFA_HUMAN ELECTRON TRANSFER FLAVOPROTEIN ALPHA-SUBUNIT PRECURSOR (ALPHA-ETF). >gnl PID e1331769 (AJ224002) electron Length = 433	gj 182251	2	442	100	100	H2CBU29
348	HBMVA11R	GARS protein [Homo sapiens] >sp Q15374 Q15374 GARS PROTEIN. Length = 433	gnl PID d100 7383	1	108	81	84	HBMVA11
349	HDPUL86R	GC kinase [Homo sapiens] >pir A53714 A53714 protein kinase (EC 2.7.1.37) BL44 - human >sp Q12851 Q12851 GC KINASE. Length = 819	gj 531820	3	317	64	65	HDPUL86
350	HTXNT16R	GTP-binding protein [Homo sapiens] >gj 577779 GTP-binding protein [Homo sapiens] >pir A55014 A55014 GTP-binding protein - human >sp P55039 DRG2_HUMAN DEVELOPMENTALLY REGULATED GTP-BINDING PROTEIN DRG2. Length = 364	gj 577779	2	463	100	100	HTXNT16
351	HBGAA13R	H (tail component;853) [Bacteriophage lambda] >pir G43008 TLBPHL minor tail protein precursor H - phage lambda Length = 853	gj 215120	1	267	97	97	HBGAA13

352	HLXNA54R	heat shock protein HSP27 [Homo sapiens] >gi 433598 28 kDa heat shock protein [Homo sapiens] >gi 1913885 heat shock protein [Homo sapiens] >pir S12102 HHU27 heat shock protein 27 - human >sp G248440 G248440 28 KDA HEAT SHOCK PROTEIN HOMOLOG FRAGMENT 2. {S Hep27 protein [Homo sapiens] >pir S66665 S66665 nuclear protein Hep27 - human >sp Q13268 HE27_HUMAN HEP27 PROTEIN (PROTEIN D). {SUB 24-280} Length = 280	gi 32478	2	256	98	98	HLXNA54
353	HCHOH37R		gi 1079566	337	564	75	81	HCHOH37
354	H2LAX93R	histone H2B [Gallus gallus] >gi 63434 histone H2B [Gallus gallus] >gi 63452 histone H2B (AA 1 - 126) [Gallus gallus] >gi 63456 histone H2B (AA 1 - 126) [Gallus gallus] >gi 63458 histone H2B [Gallus gallus] >gi 63460 histone H2B (AA 1 - 126) [Gallus gallus] homologue to elongation factor 1-gamma from A.salina [Homo sapiens] >gi 31104 elongation factor-1-gamma [Homo sapiens] >pir S22655 S22655 translation elongation factor eEF-1 gamma chain - human >sp P26641 EF1G_HUMAN ELONGATION FACTOR 1-GAMMA (EF- 1-GAMMA).	gi 211845	191	505	89	96	H2LAX93
355	HWAFW10R		gi 31102	3	434	98	98	HWAFW10

356	HBNAB19R	human complement C1r [Homo sapiens] >pir A24170 C1HURB complement subcomponent C1r (EC 3.4.21.41) precursor - human >sp P00736 C1R_HUMAN COMPLEMENT C1R COMPONENT PRECURSOR (EC 3.4.21.41). Length = 705	gi 179644	2	193	98	98	HBNAB19
357	HBGDD17R	hypothetical protein [Escherichia coli] >gi 1786774 (AE000161)orf, hypothetical protein [Escherichia coli] >pir G64788 G64788 hypothetical protein b0561 - Escherichia coli (strain K-12) Length = 247	gi 1778474	1	207	98	98	HBGDD17
358	HBIAB72R	hypoxanthine phosphoribosyltransferase [Sus scrofa] >sp P79306 P79306 HYPOXANTHINE PHOSPHORIBOSYLTRANSFERASE (FRAGMENT). Length = 85	gn P D e2919 69	2	169	81	86	HBIAB72
359	HFIEH41R	interferon-gamma induced protein [Homo sapiens] >pir I5450 I54501 interferon gamma-induced protein IFI 16 - human >sp Q16666 IFI16_HUMAN GAMMA- INTERFERON-INDUCIBLE PROTEIN IFI-16 (INTERFERON-INDUCIBLE MYELOID DIFFERENTIATION TRANSCRIPTIONAL ACTIVATOR). Le	gi 184569	5	406	96	97	HFIEH41
360	H2CBB43R	J (tail: host specificity; 1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132	gi 215125	2	400	99	99	H2CBB43

361	H2CBQ77R	J (tail:host specificity;1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132	gil215125	3	272	97	97	H2CBQ77
362	HATAO24R	J (tail:host specificity;1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132	gil215125	2	247	71	71	HATAO24
363	HOEMK06R	K (tail component;199) [Bacteriophage lambda] >pir H43009 TJBPKL tail assembly protein K - phage lambda Length = 199	gil215123	3	149	97	97	HOEMK06
364	HADCH03R	mitochondrial acetoacetyl-CoA thiolase precursor [Homo sapiens] Length = 427	gnl PID d1014983	2	256	83	83	HADCH03
365	HCHAG30R	Mta1 [Rattus norvegicus] >pir A54766 A54766 metastasis-associated protein mta-1 - rat >sp Q62599 MTA1_RAT METASTASIS-ASSOCIATED PROTEIN MTA1. Length = 703	gil595253	2	271	92	92	HCHAG30
366	HOFAD96R	NADH dehydrogenase subunit 4L [Felis catus] >sp P48931 NULM_FELCA NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 4L (EC 1.6.5.3). Length = 98	gil1098532	2	253	50	52	HOFAD96
367	H2CBX07R	Nin 221 (pept unknown;221) [Bacteriophage lambda] >pir G43011 QIBP1L multiple specificity phosphoprotein phosphatase (EC 3.1.3.-) - phage lambda >sp P03772 PP_LAMBD SERINE/THREONINE PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 221	gil215160	2	184	100	100	H2CBX07



368	HDPLN02R	nuclear corepressor KAP-1 [Homo sapiens] Length = 835	gi 1699027	149	454	90	90	HDPLN02
369	HT4FU27R	nuclear corepressor KAP-1 [Homo sapiens] Length = 835	gi 1699027	96	287	95	95	HT4FU27
370	HAEAI26R	open reading frame A; putative [Homo sapiens] Length = 84	gi 190369	109	291	78	80	HAEAI26
371	HCDAR56R	p23 [Homo sapiens] >pir A56211 A56211 progesterone receptor-related protein p23 - human >sp Q15185 Q15185 (P23). Length = 160	gi 438652	2	208	90	92	HCDAR56
372	HCDCW35R	precursor [Homo sapiens] Length = 631	gi 36049	3	155	78	84	HCDCW35
373	H2CBN76R	proteasome subunit C5 [Homo sapiens] >gnl PID e1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir S15973 SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp P20618 PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4	gnl PID d100 1116	3	464	99	99	H2CBN76
374	HAGFX49R	proteasome subunit C5 [Homo sapiens] >gnl PID e1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir S15973 SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp P20618 PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4	gnl PID d100 1116	1	288	98	100	HAGFX49

375	HNEEG64R	put. major coat protein (AA 1-341) [Bacteriophage phi-80] >pir S03314 V HBP80 major capsid protein - phage phi-80 >sp P05481 HEAD_BPPH8 MAJOR HEAD PROTEIN (GPE) (GP5) (MAJOR COAT PROTEIN), Length = 341	gij 5769	17	232	81	97	HNEEG64
376	HTXKR32R	putative nucleotide-binding protein [Homo sapiens] >pir JC4010 JC4010 nucleotide-binding protein - human >sp P53384 NBP_HUMAN NUCLEOTIDE-BINDING PROTEIN (NBP), Length = 320 putative start codon [Homo sapiens] Length = 210	gij 515644	3	374	100	100	HTXKR32
377	HAIBZ58R	rex (exclusion;279) [Bacteriophage lambda] >gij 5068 reading frame (rex) protein [Bacteriophage 434] >pir E43010 MBPAL rex A protein - phage lambda Length = 279	gij 895845	2	433	65	65	HAIBZ58
378	H6EAF46R	ribosomal protein L27a [Homo sapiens] >pir S55914 S55914 ribosomal protein L27a - human Length = 148	gij 215146	43	333	92	93	H6EAF46
379	H2LAW60R	ribosomal protein L31 [Sus scrofa] >gij 36130 ribosomal protein L31 (AA 1-125) [Homo sapiens] >gij 57115 ribosomal protein L31 (AA 1-125) [Rattus norvegicus] >pir S05576 R5HU31 ribosomal protein L31 - human >pir A26417 R5RT31 ribosomal protein L31 - rat >gn	gij 550017	3	545	88	88	H2LAW60
380	H2LAK40R		gnl PIDe2764 36	76	483	77	80	H2LAK40

381	H2LAY71R	ribosomal protein L35 [Homo sapiens] >pir G01477 G01477 ribosomal protein L35 - human Length = 123	gi 562074	70	495	100	100	H2LAY71
382	HCHAH62R	ribosomal protein L8 [Homo sapiens] >gi 57704 ribosomal protein L8 [Rattus rattus] >gi 1527178 ribosomal protein L8 [Mus musculus] >pir J00177 RSRTL8 ribosomal protein L8, cytosolic - rat >pir JN0923 JN0923 ribosomal protein L8, cytosolic - human >gi 3851	gi 433899	1	222	76	76	HCHAH62
383	H6EEF31R	ribosomal protein S2 [Rattus norvegicus] >sp O55211 O55211 RIBOSOMAL PROTEIN S2. Length = 257	gi 2920825	1	300	89	91	H6EEF31
384	HDPBT55R	RNAse L inhibitor [Mus musculus] >sp O88793 O88793 RNAse L INHIBITOR. Length = 599	gi 3273417	71	127	81	86	HDPBT55
385	HASAW80R	S. macroura Wilms tumour protein [Sminthopsis macroura] Length = 239	gi 987118	1	162	90	98	HASAW80
386	HCHAF25R	SSR alpha subunit [Homo sapiens] >pir 138246 138246 SSR alpha subunit - human Length = 286	gi 551638	2	421	95	95	HCHAF25
387	HLTHH84R	UMP synthase [Homo sapiens] >pir A30148 A30148 UMP synthase - human Length = 480	gi 340168	2	391	99	99	HLTHH84
388	H2CBU20R			39	143			H2CBU20
389	HADAA62R			3	218			HADAA62
390	HADDC09R			16	174			HADDC09
391	HAIAB75R			2	211			HAIAB75

392	HAMGA37R	3	119	HAMGA37
393	HAQA110R	1	81	HAQA110
394	HBFME95R	3	218	HBFME95
395	HBGBH24R	1	81	HBGBH24
396	HBGBT78R	1	69	HBGBT78
397	HBGCB06R	3	140	HBGCB06
398	HBGDO01R	1	156	HBGDO01
399	HBIBJ73R	3	341	HBIBJ73
400	HBJLE85R	3	398	HBJLE85
401	HBNAD53R	2	187	HBNAD53
402	HBNA163R	54	173	HBNA163
403	HCE4H65R	2	193	HCE4H65
404	HCFLJ44R	92	274	HCFLJ44
405	HCHMW05R	3	221	HCHMW05
406	HCHNR50R	2	103	HCHNR50
407	HE8DS01R	2	64	HE8DS01
408	HFEBP31R	109	276	HFEBP31

409	HLDXE36R	6	167	HLDXE36
410	HLTGV28R	181	414	HLTGV28
411	HODFW25R	42	308	HODFW25
412	HOEMQ91R	1	129	HOEMQ91
413	HOGBG56R	57	386	HOGBG56
414	HOSMT44R	2	151	HOSMT44
415	HRAEE04R	51	191	HRAEE04
416	HULFN65R	3	272	HULFN65
417	HWLVW23R	1	153	HWLVW23
418	HWLWE77R	149	289	HWLWE77

The first column of Table 1 shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention.

The second column in Table 1, provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third  
5 column in Table 1, "Gene Name," provides a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database, such as GenBank (NCBI). The great majority of the cDNA sequences reported in Table 1 are unrelated to any sequences previously described in the literature. The fourth column, in Table 1, "Overlap," provides the database accession no. for  
10 the database sequence having similarity. The fifth and sixth columns in Table 1 provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated  
15 by the nucleotide position nos. "Start" and "End". Also provided are polynucleotides encoding such proteins and the complementary strand thereto. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity) observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence.

20 The ninth column of Table 1 provides a unique "Clone ID" for a clone related to each contig sequence. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases,  
25 however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, or more of any one or more of these public ESTs are optionally excluded from the invention.

30 SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing as SEQ ID NO:1 through SEQ ID NO:418) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing as SEQ

ID NO:418 through SEQ ID NO:836) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X has uses including, but not limited to, in designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the related cDNA clone  
5 contained in a library deposited with the ATCC. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y have uses that include, but are not limited to, generating antibodies which  
10 bind specifically to the breast/ovarian cancer antigen polypeptides, or fragments thereof, and/or to the breast/ovarian cancer antigen polypeptides encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions  
15 of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over  
20 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing the related cDNA clone  
25 (deposited with the ATCC, as set forth in Table 1). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

The predicted amino acid sequence can then be verified from such deposits.  
30 Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC on:

5    **Table 2**

ATCC Deposits	Deposit Date	ATCC Designation Number
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081

each is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown in Table 5. These deposits are referred to as  
10    "the deposits" herein. The tissues from which the clones were derived are listed in Table 5, and the vector in which the cDNA is contained is also indicated in Table 5. The deposited material includes the cDNA clones which were partially sequenced and are related to the SEQ ID NO:X described in Table 1 (column 9). Thus, a clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X may include the entire coding  
15    region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Although the sequence listing lists only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to complete the sequence of the DNA included in a clone isolatable from the



ATCC Deposits by use of a sequence (or portion thereof) listed in Table 1 by procedures hereinafter further described, and others apparent to those skilled in the art.

Also provided in Table 5 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

Vectors pSport1, pCMVSPORT 1.0, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in a deposited cDNA clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in the related cDNA clone in the deposit, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the related cDNA clone (See, e.g., columns 1 and 9 of Table 1). The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the the dDNA in the related cDNA clone contained in a deposited library, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the related cDNA clone contained in a deposited library.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would unduly burden the disclosure of this application. Accordingly, for each "Contig Id" listed in the first column of Table 3, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described in the second column of Table 3 by the general formula of a-b, each of which are uniquely defined for the SEQ ID NO:X corresponding to that Contig Id in Table 1. Additionally, specific embodiments are directed to polynucleotide sequences excluding at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. for each Contig Id which may be

included in column 3 of Table 3. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example.

Table 3

Sequence/ Contig ID	General formula	Genbank Accession No.
419266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1899 of SEQ ID NO:1, b is an integer of 15 to 1913, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:1, and where b is greater than or equal to a + 14.	T68585, T68665, T86313, T86314, R12356, R31374, R32873, R37282, R84617, R85369, R99171, H48474, N23871, N58201, N74557, W90334, AA031318, AA031427, AA130231, AA256587
429114	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:2, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:2, and where b is greater than or equal to a + 14.	R20542, R42676, R42676, R20542, R61501, H08662, H77556, H97365, N24198, N33135, N74546, N93573, W02941, W52194, AA004624, AA004721, AA046710, AA235395, AA235479
506777	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 340 of SEQ ID NO:3, b is an integer of 15 to 354, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:3, and where b is greater than or equal to a + 14.	
508678	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 500 of SEQ ID NO:4, b is an integer of 15 to 514, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:4, and where b is greater than or equal to a + 14.	W37175, AA121532, AA127694
508968	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T71941, T94428, T94514, H02313, N26913, N47870, N66244, N92418, W31301, W42459, W42564, AA084031, AA126786, AA258050, AA459772

	formula of a-b, where a is any integer between 1 to 2021 of SEQ ID NO:5, b is an integer of 15 to 2035, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:5, and where b is greater than or equal to a + 14.	
509029	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1182 of SEQ ID NO:6, b is an integer of 15 to 1196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:6, and where b is greater than or equal to a + 14.	R11213, R11271, H14072, H14071, H51531, H66637, H66636, W23707, W35307, AA025586, AA025710, AA058796, AA113917
519726	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 610 of SEQ ID NO:7, b is an integer of 15 to 624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:7, and where b is greater than or equal to a + 14.	AA236015, AA236085, AA256106
522632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 287 of SEQ ID NO:8, b is an integer of 15 to 301, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:8, and where b is greater than or equal to a + 14.	
524655	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 672 of SEQ ID NO:9, b is an integer of 15 to 686, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:9, and where b is greater than or equal to a + 14.	T66495, R15869, R39696, H16266, H20784, H22599, N68150, W58001, W57856
525847	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:10, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:10, and where b is greater than or equal to a + 14.	
530306	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 549 of SEQ ID NO:11, b is an integer of 15 to 563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.	
532818	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 429 of SEQ ID NO:12, b is an integer of 15 to 443, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.	AA188990, AA191040
533385	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2424 of SEQ ID NO:13, b is an integer of 15 to 2438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.	
533532	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2333 of SEQ ID NO:14, b is an integer of 15 to 2347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	T94240, T77619, R13236, R17515, R33142, R33294, R39249, R40318, R42609, R42609, R40318, R75952, H03594, H12337, H12391, H70913, H70916, H70996, H71001, H87858, H70913, N21374, N31326, N35068, N35435, N43807, N45045, W46431, W46486, W51917, AA019546, AA018858, AA056764, AA056767, AA058441, AA058445, AA083228, AA083269, AA115939, AA122236, AA147307, AA159802,

	NO:14, and where b is greater than or equal to a + 14.	AA165015, AA165642, AA181869, AA186834, AA252269, AA255892, AA463239, AA463240
534852	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1992 of SEQ ID NO:15, b is an integer of 15 to 2006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.	T55469, T63434, R10603, R10604, H50597, H92640, H94634, W39162, W93243, W94634, W94719, N90240, AA053667, AA167312, AA253414, AA253389
537910	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:16, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.	R23785
538460	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1575 of SEQ ID NO:17, b is an integer of 15 to 1589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.	R13084, R40514, R40514, R55303, R55402, W67446
539577	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 832 of SEQ ID NO:18, b is an integer of 15 to 846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.	T49208, N35488, AA088419, AA127572, AA127649, AA156316, AA169250
548379	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2178 of SEQ ID NO:19, b	R23778, H70824

	is an integer of 15 to 2192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.	
548489	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 997 of SEQ ID NO:20, b is an integer of 15 to 1011, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.	T49861, T49862, T56225, T56367, T72170, T72948, T92867, T74728, R08625, R08719, R17408, R24674, R25174, R25378, R25997, R26800, R28401, R31330, R31589, R42642, R45259, R42642, R45259, R62552, R62553, R66386, R67726, R68781, R68878, H25120, H25121, H41115, H41190, H41191, R84227, R87629, H53386, H64419, H64476, H72640, H72641, H64419, H99301, N22341, N25846, N29370, N29843, N47918, N57261, N59763, N63813, N94171, W23786, W45524, W72111, W77797, AA010718, AA011164, AA033553, AA033554, AA062727, AA062741, AA062784, AA069811, AA075470, AA075471, AA081844, AA083492, AA084442, AA100358, AA126263, AA126354, AA136544, AA136648, AA146862, AA146863, AA179509, AA179540, AA179775, AA180492, AA181719, AA188903, AA189140, AA226959, AA227247
548595	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2005 of SEQ ID NO:21, b is an integer of 15 to 2019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.	T61537, T69836, R10679, R42501, R46798, R42501, R46798, H05289, H05822, H12239, H16816, H40312, R86905, R86985, N21432, N73268, W73102, N91565, AA033533, AA053026, AA121547, AA127684, AA190356, AA195451, AA226965, AA232522, AA258142
549337	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2008 of SEQ ID NO:22, b is an integer of 15 to 2022, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.	
549777	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1112 of SEQ ID NO:23, b	T81557, R27931, R38730, R39493, R39494, R66845, R67942, R69099, R69214, R69613, R69703, R69740, R72430, R72478, R73090, R73091, R73872, R73955, R82662, R82715, H01096, H01097, H72113, N76139, W58493, W72884, W74409, W94644, W92532,



	is an integer of 15 to 1126, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.	AA022916, AA022917, AA039661, AA039660, AA043439, AA054965, AA152376, AA148360, AA181225, AA188435
553091	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2584 of SEQ ID NO:24, b is an integer of 15 to 2598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.	
553827	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 397 of SEQ ID NO:25, b is an integer of 15 to 411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.	
556350	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:26, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.	T70920, R01856, R37402, H21077, H21531, R94734, N29364, N32255, N80553, W07675, W58340, W58661, W67208, W67352, AA039658, AA039659, AA046392, AA055650, AA058365, AA070442, AA088882, AA102056, AA134144, AA165363, AA171617, AA173761, AA173771, AA252260, AA464575, AA464679
556351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1889 of SEQ ID NO:27, b is an integer of 15 to 1903, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.	T70981, R01855, R13494, H21076, H24431, H24460, R94817, N47912, AA040086, AA040133, AA055706, AA056162, AA058484, AA102055, AA102304, AA130304, AA173608, AA195879
557007	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H13846, H13894, H16354, H20742, H20743, R97935, R97936, H87445, N29633, AA015991, AA045671, AA045670, AA099154, AA099252

	sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO:28, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.	
558140	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1313 of SEQ ID NO:29, b is an integer of 15 to 1327, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.	T62991, W58535, W58500, AA053629, AA083878, AA112892, AA157250, AA157345, AA194089, AA253436, AA250750
558456	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of SEQ ID NO:30, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.	
558708	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1094 of SEQ ID NO:31, b is an integer of 15 to 1108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.	R38385, W24640, W48793, W49619
574789	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:32, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.	N49156

578203	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 541 of SEQ ID NO:33, b is an integer of 15 to 555, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.	AA149853
585385	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 333 of SEQ ID NO:34, b is an integer of 15 to 347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.	
588869	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 736 of SEQ ID NO:35, b is an integer of 15 to 750, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.	
597076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:36, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.	
598656	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1521 of SEQ ID NO:37, b is an integer of 15 to 1535, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.	
611880	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 281 of SEQ ID NO:38, b is an integer of 15 to 295, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.	
614329	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1286 of SEQ ID NO:39, b is an integer of 15 to 1300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.	T49777, T51334, T49778, T66835, T66836, T78401, R33579, R33684, R34361, R34476, R72556, R75702, H01591, H02719, H13232, H13599, H13942, H13943, H63376, H80729, H80730, H89353, H89539, H99395, N26995, N32930, N40116, N42081, N50408, N50460, N63978, N67308, N92847, W46413, AA126994, AA128141, AA146958, AA146957, AA425764
616066	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 201 of SEQ ID NO:40, b is an integer of 15 to 215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.	
620956	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 460 of SEQ ID NO:41, b is an integer of 15 to 474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.	
621889	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 411 of SEQ ID NO:42, b is an integer of 15 to 425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.	
624017	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1173 of SEQ ID NO:43, b is an integer of 15 to 1187, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.	T61010, AA071044, AA088260, AA098798, AA102017, AA100707, AA111883, AA113305, AA121495, AA133235, AA131438, AA132011, AA132866, AA143457, AA146581, AA146805, AA146928, AA155613, AA155609, AA158090, AA158263, AA164694, AA165591, AA176429, AA226820
651784	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:44, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.	W32583, W68240, W94174, AA251670, AA252011, AA252266, AA425209
651826	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1485 of SEQ ID NO:45, b is an integer of 15 to 1499, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.	T47384, T47385, T60137, T60194, T71947, T95050, T95146, R25340, R25476, R26117, R26301, R27566, R27664, R28180, R33393, R35872, R35873, R36483, R48329, R48438, R62139, R62244, R66007, R66008, R66764, R70718, R70719, R73674, R73761, R74132, R76569, R76643, R77265, R77312, R78827, R79686, R79687, R81316, R81751, H00804, H00891, H01415, H01416, H02522, H03673, H13925, H13926, H24743, H26369, H26727, H26728, H27132, H27480, H27663, H28192, H28235, H41929, H41977, H42604, H43209, H43258, H45278, H45348, H53585, H53906, H61785, H61786, H78337, H78338, H87337, H87871, H95183, N27090, N27092, N40499, N40502, N99158, W24165, W60193, AA039817, AA041344, AA074512, AA079058, AA079156, AA079157, AA085829, AA085974, AA100095, AA113304, AA142843, AA149898, AA156331, AA157820, AA157895, AA158552, AA159177, AA176093, AA179607, AA179608, AA176333, AA187637, AA186769, AA188622, AA188742, AA188975
653282	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 379 of SEQ ID NO:46, b is an integer of 15 to 393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.	
657122	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 224 of SEQ ID NO:47, b is an integer of 15 to 238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.	
661442	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 925 of SEQ ID NO:48, b is an integer of 15 to 939, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.	R18101, AA424721
664914	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1757 of SEQ ID NO:49, b is an integer of 15 to 1771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.	T86944, T87027, R11421, T81153, T81380, R17243, R17453, R19171, R27826, R27927, R35295, R35940, R41854, R42800, R48191, R48192, R49457, R51209, R52247, R53413, R41854, R42800, R49457, R55257, R55475, R59472, R71390, R81811, R81915, H05137, H07974, H30702, H42552, H57923, H58015, N71127, N74282, N75329, N93224, W01557, W04382, W04780, W23438, W35253, W38865, AA176204, AA194869, AA199875, AA251414
666654	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:50, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:50, and where b is greater than or equal to a + 14.	
667084	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1621 of SEQ ID NO:51, b is an integer of 15 to 1635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.	R71869, R71870, H22387, H27160, H46592, H61204, H62108, N25274, N94410, AA026642, AA069188, AA069189, AA076423, AA076388, AA076533, AA076540, AA122346, AA121039, AA121092, AA133121, AA143471, AA143470, AA143728, AA156363, AA156404, AA158498, AA159190, AA159201, AA159286, AA160335, AA159837, AA159573, AA160367, AA159548, AA160456, AA160697, AA160789, AA179329, AA181540, AA182669, AA186881, AA186887, AA188535, AA188540, AA190669, AA190973, AA191557, AA235457, AA458511, AA418203
667380	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1766 of SEQ ID NO:52, b is an integer of 15 to 1780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.	T87574, R10276, R10277, T79847, R49790, R49832, R59538, R59539, R86940, R87067, R87722, R98577, R98578, R99022, R99795, H72692, H93036, H93942, H93941, N54059, N62326, N64719, N66726, N73888, N74171, N91734, N93505, W02054, W03949, W04337, W21317, AA192562, AA192563, AA223984, AA224049
669530	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:53, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.	T49160, T49161, H41659, R88196, W60799, W60930, AA046915, AA046972, AA069703, AA464334
671315	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1930 of SEQ ID NO:54, b is an integer of 15 to 1944, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.	
671993	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 980 of SEQ ID NO:55, b is an integer of 15 to 994, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.	
674618	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 314 of SEQ ID NO:56, b is an integer of 15 to 328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.	
675027	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1475 of SEQ ID NO:57, b is an integer of 15 to 1489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.	T86474, AA133454, AA203346
677202	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:58, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.	T47486, T47487, T47666, T50413, T50493, T50519, T51852, T53234, T57067, T60776, T40856, T93579, T94432, T94435, T96391, R43542, R43542, H21618, H73240, H88867, H88868, H89122, H88868, H89122, N21997, N22243, N22815, N45720, N48998, N52063, N59239, N62103, N66419, N66708, N66782, N67139, N67283, N67447, N68047, N70159, N71198, N74676, N76707, N78333, N80016, N92971, N93518, W05738, W45694, W48845, W80602, AA057801, AA063330, AA064827, AA065165, AA065178, AA065179, AA069552, AA070491, AA070949, AA070969, AA071333, AA071358, AA074331, AA081280, AA111928, AA112051, AA132018, AA132121, AA147357, AA157065, AA157085, AA157890, AA160054, AA181729, AA182765, AA187698, AA186444, AA196168, AA196244, AA224187
678504	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 726 of SEQ ID NO:59, b is	



	an integer of 15 to 740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.	
678985	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:60, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.	
682161	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:61, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.	
683476	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 604 of SEQ ID NO:62, b is an integer of 15 to 618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.	
691146	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1124 of SEQ ID NO:63, b is an integer of 15 to 1138, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.	T48865, T48866, T48901, T47562, T48902, T54258, T54365, T69783, T70768, R08012, R09058, R09059, T83437, T84082, T99021, R09059, R19174, R21551, R22562, R28286, R48757, R48758, R49683, R49683, R62406, R62407, R70222, R75607, R77000, R78400, R78401, R80802, H02840, H03734, H24549, H26291, H26447, H27912, H43630, H47817, R83903, R83904, R94147, H49533, H49773, H50716, H50820, H87446, H87553, H93471, H93472, H98814, N22867, N32137, N32762, N34334, N35009, N36932, N43763, N46205, N52251, N56805, N72290, N95794, W02713, W02886, W17176, W24905, W25571, W25688,

		W67795, W72687, W72962, W77793, W79704, W81376, W86301, W86316, AA025519, AA025959, AA026653, AA029556, AA029704, AA079472, AA121306, AA136679, AA148681, AA148680, AA181745, AA425923
693589	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 404 of SEQ ID NO:64, b is an integer of 15 to 418, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.	
694991	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2822 of SEQ ID NO:65, b is an integer of 15 to 2836, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.	
698303	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2291 of SEQ ID NO:66, b is an integer of 15 to 2305, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.	T83582, T84417, T85606, R66380, R67111, R76298, H96019, H96020, N25659, N25661, N34260, N34263, N70618, W05500, W15421, W23670, W39659, AA015855, AA033569, AA033570, AA044566, AA044583, AA178933, AA179025
698669	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1893 of SEQ ID NO:67, b is an integer of 15 to 1907, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.	T47115, T47116, R48786, R48893, R55495, R71847, R78934, R79033, R82776, H26587, H27077, R97760, H59232, H79115, H79116, N22948, N23658, N26858, N28757, N39967, N71599, W24648, W60157, W67490, W67491, W67815, W72921, W94215, AA009634, AA026899, AA026900, AA029244, AA029040, AA031846, AA031847, AA032073, AA034285, AA034992, AA036865, AA037006, AA040908, AA039990, AA040521, AA040522, AA040773, AA043726, AA044071, AA044182, AA042948, AA043067, AA046606, AA046721, AA062914, AA074334, AA076039, AA076203, AA079763, AA079764, AA082550, AA085926, AA099318,

		AA099836, AA102385, AA101039, AA101040, AA112571, AA112572, AA114828, AA114951, AA128001, AA128082, AA126986, AA128134, AA128459, AA129910, AA131403, AA131503, AA147437, AA147438, AA150961, AA151051, AA156785, AA156855, AA157912, AA157913, AA158544, AA158545, AA158554, AA158553, AA211822, AA460840, AA461144
705696	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:68, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.	H20141, H20156, H20236, H20250, H49965, H50007, H50487, W92252, AA045116, AA134141, AA142968
706393	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1136 of SEQ ID NO:69, b is an integer of 15 to 1150, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.	T48975, T51242, T51357, T59673, T59807, T62725, T62875, T72330, T97577, R01168, R21893, R22365, R35745, R41863, R41863, R63676, R65881, R72862, R73334, R75659, R75767, H02871, H03430, H03512, H14924, H23660, H30020, H30277, H39675, H40069, H40278, H40526, H41667, H41700, H43170, H43670, H45130, H45172, H45173, H45433, H46542, H46952, H46953, H62390, H78695, H78777, H84781, H85405, H92309, N20534, N33402, N38945, N57790, N57945, N59752, W94488, W94489, AA044423, AA043057, AA081370, AA081371, AA099447, AA112623, AA112622, AA143199, AA143214, AA149467, AA149553, AA157049, AA157201, AA157952, AA157953, AA158049, AA158435, AA158837, AA158841, AA161074, AA161078, AA180395, AA251447, AA419021, AA428783, AA429093
707357	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 330 of SEQ ID NO:70, b is an integer of 15 to 344, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.	
707360	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 434 of SEQ ID NO:71, b is an integer of 15 to 448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.	
707375	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2811 of SEQ ID NO:72, b is an integer of 15 to 2825, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.	T54138, T65139, T65330, T80324, T83140, R00512, R00612, R19513, R31469, R31470, R47795, R77921, R78022, R80012, H02327, H02429, H06404, H06405, H08607, H08608, H14264, H18370, H19266, H19267, H21399, H21471, H47094, H47185, R85467, R87496, R87501, R87581, R88189, R88226, R88227, N23376, N32357, N58463, N66212, N93661, N99103, W19083, W24383, W68601, W68602, W68723, W68745, AA016149, AA040296, AA056973, AA135439, AA135519, AA135580, AA135856, AA158858, AA161122, AA226730, AA226764, AA227471, AA227481, AA232259
707754	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 496 of SEQ ID NO:73, b is an integer of 15 to 510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.	
711172	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 444 of SEQ ID NO:74, b is an integer of 15 to 458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.	
712248	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 363 of SEQ ID NO:75, b is an integer of 15 to 377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or	

	equal to $a + 14$ .	
715445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 2056 of SEQ ID NO:76, $b$ is an integer of 15 to 2070, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where $b$ is greater than or equal to $a + 14$ .	T88778, T97557, T97604, R17189, R27615, R30849, R41740, R48616, R41740, H12351, R93768, R98882, R98972, H59983, N23156, N32736, N34539, N55086, N62785, N67224, N77297, N78823, N79734, W07252, W90651, AA037793, AA037794, AA055196, AA055286, AA113425, AA233917, AA234165, AA258602, AA258548, AA426581, AA429080
716362	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 983 of SEQ ID NO:77, $b$ is an integer of 15 to 997, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where $b$ is greater than or equal to $a + 14$ .	
716835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 1319 of SEQ ID NO:78, $b$ is an integer of 15 to 1333, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where $b$ is greater than or equal to $a + 14$ .	
716947	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 546 of SEQ ID NO:79, $b$ is an integer of 15 to 560, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where $b$ is greater than or equal to $a + 14$ .	
717685	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 3189 of SEQ ID NO:80, $b$ is an integer of 15 to 3203, where both $a$	T54040, N35800, W45088, AA122232, AA121109, AA126030, AA126152, AA155618, AA155656

	and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.	
719755	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1696 of SEQ ID NO:81, b is an integer of 15 to 1710, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.	
720389	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1365 of SEQ ID NO:82, b is an integer of 15 to 1379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.	
720903	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 664 of SEQ ID NO:83, b is an integer of 15 to 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.	
721348	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2789 of SEQ ID NO:84, b is an integer of 15 to 2803, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.	
721562	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 1264 of SEQ ID NO:85, b is an integer of 15 to 1278, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.	
722775	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2571 of SEQ ID NO:86, b is an integer of 15 to 2585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.	
724463	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 371 of SEQ ID NO:87, b is an integer of 15 to 385, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.	
727501	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2486 of SEQ ID NO:88, b is an integer of 15 to 2500, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.	
728418	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:89, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.	
728920	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:90, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.	
732958	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 773 of SEQ ID NO:91, b is an integer of 15 to 787, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.	
733134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1643 of SEQ ID NO:92, b is an integer of 15 to 1657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.	T49547, T49558, T49559, T49560, T49561, T49649, T49650, T70062, T70129, T75532, T95137, R17573, T27052, R19790, R42912, R52618, R53272, R42912, R59922, R59923, R65930, H08841, H08925, H47546, H47547, H47774, H47784, H48119, H64949, H64950, H69959, H69960, H80517, H80569, H81281, H81337, H87618, H87619, H88959, H89042, H95657, H95712, H95729, H88959, H98860, N20108, N23582, N27446, N34733, N49675, N51841, N75517, N78965, N93975, W05310, W17334, W40344, W52084, W52929, W72818, W72819, W86046, W92307, W92294, AA009783, AA009892, AA022930, AA022980, AA024699, AA024734, AA037408, AA045887, AA045888, AA062821, AA081026, AA082088, AA082420, AA102801, AA199861, AA199931, AA220961, AA223217, AA223456, AA224153, AA224177, AA224137, AA224138, AA224341, AA232349, AA232533, AA232117, AA458900, AA459095, AA463299
734099	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 471 of SEQ ID NO:93, b is an integer of 15 to 485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or	R22895, H87448



	equal to $a + 14$ .	
734599	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 750 of SEQ ID NO:94, b is an integer of 15 to 764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to $a + 14$ .	
736019	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 693 of SEQ ID NO:95, b is an integer of 15 to 707, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to $a + 14$ .	T41219, T50359, T56829, T58426, T58458, T60928, T60984, T64158, T64287, R27157, H03484, H03579, H22546, H22547, H28310, H44067, H44146, R83796, H48481, H48645, H57243, H66162, H66163, H82370, N21110, N21188, N27461, N29155, N29743, N31124, N32398, N39884, N56818, N57165, N57228, N57403, N68904, N73978, N77833, N93027, N93818, N67112, W00894, W00923, W02234, W16676, W21379, W44969, AA064843, AA070697, AA070876, AA071332, AA071265, AA076379, AA076308, AA079524, AA079572, AA081231, AA081401, AA083774, AA083775, AA130308, AA130309, AA132056, AA132160, AA143132, AA146882, AA146883, AA165057, AA164722, AA166939, AA181133, AA187371, AA187804, AA188118, AA186447, AA186448, AA187105, AA187150, AA188273
738268	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:96, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to $a + 14$ .	T48287, T48288, T54477, T54511, R34064, R36907, R49496, R49496, R75625, R75724, H12225, H16384, H19466, H19543, H42166, H42988, H54780, H99297, N22733, N26471, N74933, N93468, W15461, W47542, W47590, N90997, AA010700, AA010701, AA056728, AA088699, AA126219, AA132934, AA156291, AA165516, AA165558, AA176293, AA173448, AA189056, AA233515, AA459831, AA460011
738911	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 644 of SEQ ID NO:97, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to $a + 14$ .	H22593, H52836

739226	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 235 of SEQ ID NO:98, b is an integer of 15 to 249, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.	T57824, N63155, AA027845
739527	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 738 of SEQ ID NO:99, b is an integer of 15 to 752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.	
740710	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3045 of SEQ ID NO:100, b is an integer of 15 to 3059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.	
742980	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1668 of SEQ ID NO:101, b is an integer of 15 to 1682, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.	T71993, R12901, R40053, H14591, H14696, R83485, H50584, H50585, H89958, H89966, H89973, H89980, N26005, N34777, N36638, N36637, N44503, N67682, N76121, N79613, W03491, W05571, W31276, W49653, W49727, AA009708, AA009798, AA035612, AA042894, AA043030, AA062953, AA115370, AA133278, AA181268, AA181269, AA193206
744331	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:102, b is an integer of 15 to 938, where both a and b correspond to the positions of	R25354, R49789, R71735, R71740, H73502, H79224, H87423, H99515, H99516, N24751, N32707, N44511, N52325, N67764, N75095, N93879, W40372, W69127, W69094, W74698, W74736, AA026984, AA035176, AA149088, AA262739, AA464357, AA430724

	nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.	
744751	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1998 of SEQ ID NO:103, b is an integer of 15 to 2012, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.	
745750	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:104, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.	
746285	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2283 of SEQ ID NO:105, b is an integer of 15 to 2297, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.	T87719, T87928, R99975, R99976, H64714, H65205, H92423, H65205, N47296, N48612, N58085, N58926, N64294, N64508, N72401, N80294, N93405, W04791, W21447, W94582, W95317, AA024856, AA024939, AA037672, AA037673, AA070416, AA075508, AA075507, AA101263, AA148029, AA147953, AA169726, AA171461, AA173095, AA464821
746416	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 428 of SEQ ID NO:106, b is an integer of 15 to 442, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.	
747851	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	N44767, W44754

	between 1 to 1005 of SEQ ID NO:107, b is an integer of 15 to 1019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.	
750632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 697 of SEQ ID NO:108, b is an integer of 15 to 711, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.	H48882, W23677, W35110, AA133857
751315	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:109, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.	
754009	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 781 of SEQ ID NO:110, b is an integer of 15 to 795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to a + 14.	
754634	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1318 of SEQ ID NO:111, b is an integer of 15 to 1332, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.	N21429
756637	Preferably excluded from the present invention are one or more	N44651, W76461

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:112, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.	
756833	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1676 of SEQ ID NO:113, b is an integer of 15 to 1690, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.	
756878	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 606 of SEQ ID NO:114, b is an integer of 15 to 620, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.	R12122
757332	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 528 of SEQ ID NO:115, b is an integer of 15 to 542, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.	
760835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:116, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or	

	equal to $a + 14$ .	
761760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 714 of SEQ ID NO:117, $b$ is an integer of 15 to 728, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where $b$ is greater than or equal to $a + 14$ .	
762520	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 934 of SEQ ID NO:118, $b$ is an integer of 15 to 948, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where $b$ is greater than or equal to $a + 14$ .	T86617, T86618, R47814, R49961, R71921, R71968, H28225, H28275, R94939, R95025, R97173, R97174, R99726, R99904, H52435, H52436, H58879, H58880, H66345, H66395, H80709, H80710, W87663, W87664, AA046620, AA046867, AA055456, AA102380, AA121314, AA150579, AA197300
764461	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 197 of SEQ ID NO:119, $b$ is an integer of 15 to 211, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where $b$ is greater than or equal to $a + 14$ .	
764517	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 1294 of SEQ ID NO:120, $b$ is an integer of 15 to 1308, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where $b$ is greater than or equal to $a + 14$ .	
765132	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 2502 of SEQ ID NO:121, $b$ is an integer of 15 to 2516, where both	

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.	
765667	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1125 of SEQ ID NO:122, b is an integer of 15 to 1139, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.	T81691, N27595
767113	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2100 of SEQ ID NO:123, b is an integer of 15 to 2114, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:123, and where b is greater than or equal to a + 14.	
767204	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 569 of SEQ ID NO:124, b is an integer of 15 to 583, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.	
767400	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1973 of SEQ ID NO:125, b is an integer of 15 to 1987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.	
767962	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T59753, R21255, R21256, R23274, R23364, R71913, R71956, H12633, H12686, H99087, N26954, N33518, N43798, N62998, N66835, N71124, N71156, N74144, N79907, W01554,

	formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:126, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:126, and where b is greater than or equal to a + 14.	W05537, W19994, W44368, W46357, W46193, W47163, W47284, W52537, W55854, W80804, W80878, W92021, W92022, N90420, AA002178, AA022578, AA022579, AA029899, AA029987, AA034181, AA036856, AA036913, AA043237, AA043566, AA071518, AA082340, AA122159, AA120962, AA146944, AA147449, AA148081, AA151266, AA151267, AA156459
768040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1220 of SEQ ID NO:127, b is an integer of 15 to 1234, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.	
769956	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 849 of SEQ ID NO:128, b is an integer of 15 to 863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.	R68817, R68925, R75906, H14626, H82146, H93109, H93237, N32098, N35721, N45410, N75570, W03043, W04850, AA029607, AA262861, AA463956, AA464092
770133	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1224 of SEQ ID NO:129, b is an integer of 15 to 1238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.	
770289	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 365 of SEQ ID NO:130, b is an integer of 15 to 379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.	



771964	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1772 of SEQ ID NO:131, b is an integer of 15 to 1786, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.</p>	<p>T53984, T55243, T51230, T77632, T91326, T80819, T81219, T84909, T95454, T97320, T99226, T99269, R16575, R16634, R19765, R22987, R23096, R33095, R33188, R37437, R39255, R45185, R45185, R62594, R62642, H03891, H03892, H08679, H08680, H20556, H20650, H46154, H46155, R88298, R90733, R90759, R92224, R92332, R97325, H57663, H58503, H61709, H61913, H62747, H66685, H68924, H68954, H80053, H83342, H95786, H96135, N20464, N20472, N24026, N25491, N35235, N35419, N38769, N44900, N48399, N53146, N55089, N55095, N57767, N58580, N59732, N63942, N70290, N71759, N74938, N77300, N98411, W23555, W52690, W52160, W56557, W56635, W56598, W56594, W73408, W74230, W79843, W93916, AA031492, AA070868, AA071019, AA088788, AA100685, AA112926, AA176829, AA176851, AA193034, AA194065, AA194180, AA194579, AA194703, AA195416, AA195532, AA233792, AA233783, AA233900, AA233920, AA234128, AA234169, AA252704, AA252831, AA416743, AA418391, AA418440</p>
772582	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 960 of SEQ ID NO:132, b is an integer of 15 to 974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.</p>	
773387	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 620 of SEQ ID NO:133, b is an integer of 15 to 634, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.</p>	
773827	<p>Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1841 of SEQ ID NO:134,</p>	

	b is an integer of 15 to 1855, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.	
774108	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:135, b is an integer of 15 to 917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.	T96288, R31388, R32886, R63543, R63597, R75811, R75812, H20285, H20509, H20599, H21238, H24872, H29854, H29945, H41103, H41208, H44188, H44189, R85628, R91367, H83459, H83571, H97165, H97164, N25639, N29652, N29777, N32407, N32413, N32580, N32835, N41918, N42281, N56607, N57152, N57196, N69818, N70613, N93340, N93928, N94454, W24358, W25163, W30800, W37904, W37964, W40428, W68631, W68632, W70339, W80994, W81096, W81716, W81253, W81543, W81544, W94206, AA004372, AA011346, AA016002, AA028888, AA029626, AA029627, AA044028, AA044350, AA062804, AA081035, AA131270, AA131354, AA131371
774636	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1257 of SEQ ID NO:136, b is an integer of 15 to 1271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14.	T54747, T69827, R14146, R50592, R55502, R73615, R73937, H41540, R84981, R85103, R87495, R88553, R88554, R88556, R88818, R88839, R89675, R91235, H51003, H51004, H51581, H79057, N70799, W02680, AA232327, AA232417, AA464467
775339	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2003 of SEQ ID NO:137, b is an integer of 15 to 2017, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to a + 14.	
775582	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 923 of SEQ ID NO:138, b is an integer of 15 to 937, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or	T62486, T62631, H14642, R85991, H73603, N54912, N68727, N80228, N91617, W38518, W67302, W67418, AA171395, AA214500, AA215291, AA464035

	equal to $a + 14$ .	
775779	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2745 of SEQ ID NO:139, b is an integer of 15 to 2759, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:139, and where b is greater than or equal to $a + 14$ .	
777809	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1227 of SEQ ID NO:140, b is an integer of 15 to 1241, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to $a + 14$ .	
778927	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3391 of SEQ ID NO:141, b is an integer of 15 to 3405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to $a + 14$ .	T50777, T50939, R11800, R19713, R31403, R32898, R44269, R44269, R55431, R60041, R60103, R69554, R74340, R74434, H20427, H26615, H26660, H42495, H43482, R85644, H51488, H68618, N58157, N58231, N77611, W39692, W45048, W56828, W57633, AA052900, AA057808, AA074705, AA122120, AA121079, AA121231, AA259051, AA464470
779262	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2254 of SEQ ID NO:142, b is an integer of 15 to 2268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to $a + 14$ .	R11844, R71241, R71292, H00159, H88551, H90726, H98059, N28770, N58442, N78033, W32671, AA035075, AA112651, AA112652, AA130035, AA215309, AA251209
779392	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1743 of SEQ ID NO:143, b is an integer of 15 to 1757, where both	R25284, R36255, R36256, R42970, R46635, R42970, R46635, H28773, N52867, N70541, N77890, W05403, W05783, AA085067, AA085066, AA204650, AA210753, AA211713, AA251462, AA252456, AA460350, AA460780

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to a + 14.	
780149	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1048 of SEQ ID NO:144, b is an integer of 15 to 1062, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to a + 14.	
780583	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1016 of SEQ ID NO:145, b is an integer of 15 to 1030, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to a + 14.	
780960	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:146, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to a + 14.	
781469	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2664 of SEQ ID NO:147, b is an integer of 15 to 2678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to a + 14.	T95791, H18820, H19074, H22604, H40723, H45802, H46056, H47074, H47156, H86819, H86886, H88675, H88724, H88972, H89058, H88972, N28987, N36053, N39668, N47281, W19145, W68543, W68544, N91577, AA044679, AA044896, AA430011
781556	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T94861, T94906, R21516, R26869, R27098, R36258, R37965, R37966, R78172, H03413, H04116, H14531, H45546, R96826, R98130, N51409, N52365, N64272, N74939, N75136,

	formula of a-b, where a is any integer between 1 to 1014 of SEQ ID NO:148, b is an integer of 15 to 1028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14.	W23556, W35208, AA187823, AA191525, AA429367
781771	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:149, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14.	T95420, T99529, R50341, R52125, R72608, R72630, R72677, R72701, H26733, H26734, H30106, H59788, H82441, N75150, W42750, W42840
782033	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:150, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14.	H53100, H53207, H97410, H98035, N30753, N68541, W42491, W42641, W57808, AA046603, AA046753, AA136886, AA136997, AA143419, AA143420
782105	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:151, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14.	R97486, H72940, W90139
782122	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1635 of SEQ ID NO:152, b is an integer of 15 to 1649, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14.	T54379, T60348, T61029, T54271, T57801, R10793, T78907, T78959, R49078, R55635, R67844, R67845, R69587, R72600, R72666, H04742, H04830, H16978, H24654, H26129, H26308, H26395, H26467, H28100, H28205, H28252, H28895, H28896, H30485, H39554, H42595, H42603, H42662, H43740, H44345, H44346, H44546, H44547, H44960, H45012, H45860, R88120, R88214, H51204, H58080, H58081, H64553, H64654, H70033, H70034, H86451, H70034, H99833, N24525, N29867, N30752, N35500, N39259, N42463, N44804,

		N52550, N53985, N57289, N58726, N63349, N67624, N67663, N68157, N70299, N80615, N93230, N94595, N98489, W19633, W23803, W25087, W31034, W37981, W37982, W42579, W44389, W49677, W57614, W57871, W58142, W67781, W67840, W68147, W68474, W68699, W68791, W69717, W80749, W80837, N89879, AA025233, AA025568, AA025686, AA026020, AA033846, AA039625, AA039693, AA046842, AA047013, AA057608, AA057676, AA064637, AA064680, AA074448, AA083591, AA098837, AA102142, AA113374, AA113402, AA115525, AA114948, AA128972, AA128973, AA133142, AA146949, AA148086, AA149283, AA149377, AA160012, AA160688, AA172144, AA180932, AA182561
783135	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 646 of SEQ ID NO:153, b is an integer of 15 to 660, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14.	
783245	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 591 of SEQ ID NO:154, b is an integer of 15 to 605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14.	
783247	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 681 of SEQ ID NO:155, b is an integer of 15 to 695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14.	AA155638
783413	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	H58751, H93683, H93684, N93167, W19186, W19958, W38771, N91367

	sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:156, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14.	
784407	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1113 of SEQ ID NO:157, b is an integer of 15 to 1127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14.	
784548	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:158, b is an integer of 15 to 1282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14.	
785075	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1491 of SEQ ID NO:159, b is an integer of 15 to 1505, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:159, and where b is greater than or equal to a + 14.	
785677	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 722 of SEQ ID NO:160, b is an integer of 15 to 736, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14.	

786238	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 981 of SEQ ID NO:161, b is an integer of 15 to 995, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14.	
786389	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:162, b is an integer of 15 to 1125, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14.	
786929	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:163, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14.	
786932	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1628 of SEQ ID NO:164, b is an integer of 15 to 1642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14.	
787078	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1101 of SEQ ID NO:165, b is an integer of 15 to 1115, where both a and b correspond to the positions of	



	nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14.	
787139	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:166, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14.	
787283	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:167, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14.	R22724
788761	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1012 of SEQ ID NO:168, b is an integer of 15 to 1026, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14.	
788988	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 760 of SEQ ID NO:169, b is an integer of 15 to 774, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14.	
789092	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	AA234588

	between 1 to 388 of SEQ ID NO:170, b is an integer of 15 to 402, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14.	
789298	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 782 of SEQ ID NO:171, b is an integer of 15 to 796, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14.	
789299	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:172, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14.	
789718	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 642 of SEQ ID NO:173, b is an integer of 15 to 656, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:173, and where b is greater than or equal to a + 14.	
789957	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1877 of SEQ ID NO:174, b is an integer of 15 to 1891, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to a + 14.	T51260, T61941, T62167, T77034, T90753, R38108, N32708, N92379, W24621, W42543, W42478, AA128007, AA128031, AA134234, AA424998
789977	Preferably excluded from the present invention are one or more	T56442, T78292, R37940, R56008, R56009, R56573, R56574, H11080, N34431, N48665,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2147 of SEQ ID NO:175, b is an integer of 15 to 2161, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:175, and where b is greater than or equal to a + 14.	AA010749, AA011177, AA070806, AA070882, AA146859, AA147636, AA147691, AA164223, AA164224, AA210729, AA210859, AA243063, AA243070, AA464493, AA464494
790285	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2397 of SEQ ID NO:176, b is an integer of 15 to 2411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to a + 14.	T66279, T66328, T84164, T85098, R24232, R24233, H03657, H03658, H98526, H98556, H99618, N22728, N29400, N32172, N33953, N41460, N69471, N70552, N73722, W03893, W44579, W72407, W76486, W78102, W79410, N90963, AA044816, AA044841, AA086039, AA086121, AA088877, AA102298, AA130887, AA131529, AA131603, AA181784, AA182515, AA190450, AA191392, AA223757
790509	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1324 of SEQ ID NO:177, b is an integer of 15 to 1338, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to a + 14.	T68040, H17760, AA101036, AA129837
790775	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1600 of SEQ ID NO:178, b is an integer of 15 to 1614, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to a + 14.	N25320, N31432, W81044, W81097
790888	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4278 of SEQ ID NO:179, b is an integer of 15 to 4292, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or	R14550, R15204, T26493, R21597, R22908, R23010, R41211, R41649, R43371, R41211, R41649, R43371, R58989, R59048, H05739, H05845, H17266, H17265, H23579, H44104, H46505, H47043, H58955, H59002, H73676, H73730, H80078, H82275, H82289, H82399, H82381, H97810, H98133, H98737, N23117, N24310, N25196, N25265, N27792, N28735, N29893, N33395, N33904, N36066, N36839, N42542, N46060, N51230, N59535, N67737,

	equal to $a + 14$ .	N73641, N78481, N78694, W03555, W15202, W52445, W52723, W95124, AA047257, AA057142, AA204699, AA251464, AA430598
791506	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 229 of SEQ ID NO:180, b is an integer of 15 to 243, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:180, and where b is greater than or equal to $a + 14$ .	
791649	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 799 of SEQ ID NO:181, b is an integer of 15 to 813, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to $a + 14$ .	
791802	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 808 of SEQ ID NO:182, b is an integer of 15 to 822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:182, and where b is greater than or equal to $a + 14$ .	
792002	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1081 of SEQ ID NO:183, b is an integer of 15 to 1095, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:183, and where b is greater than or equal to $a + 14$ .	T49735, T49736, T95310, T95391, T99384, T99612, R63493, R63494, H27739, R91698, R92136, H52608, H57619, H58464, H61415, H62139, H69019, H87167, H87669, N21358, N70307, N79596, W19063, W58498, W58651, W79687, W81289, AA099849, AA099972, AA232767
792291	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	T55436, R21797, R22403, R22452, R22916, R23020, R76901, R77068, H22573, H25752, H25866, R83900, H50717, H50821, H64026, H64791, H95702, N64545, N69769, N74704, N80341, W05092, W79489, W79634,

	between 1 to 3661 of SEQ ID NO:184, b is an integer of 15 to 3675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14.	AA005055, AA005007, AA025043, AA036711, AA037127, AA043916, AA055100, AA063627, AA069142, AA069230, AA069323, AA069376, AA112277, AA112531, AA115279, AA151238, AA151239, AA151582, AA149398, AA149961, AA150069, AA158029, AA158321, AA158692, AA158693, AA161232, AA236787, AA236834, AA256776, AA261961
792371	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1026 of SEQ ID NO:185, b is an integer of 15 to 1040, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14.	
792660	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 803 of SEQ ID NO:186, b is an integer of 15 to 817, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14.	T59054, T86590, T83271, R48677, R53483, R53482, R62329, R62330, R66651, R67372, R69095, R69210, R71144, R82632, R82676, H15764, H15765, H19518, H19605, H27898, H42872, H42936, H49329, H49330, H50062, H50061, H87268, H87324, H96667, N22675, N92574, W37223, W37563, W38866, W61119, W65380, AA035095, AA035635, AA037254, AA054951, AA062973, AA082301, AA132472
792782	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1066 of SEQ ID NO:187, b is an integer of 15 to 1080, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14.	
792890	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1272 of SEQ ID NO:188, b is an integer of 15 to 1286, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14.	AA251351

792931	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1724 of SEQ ID NO:189, b is an integer of 15 to 1738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:189, and where b is greater than or equal to a + 14.	
792943	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:190, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to a + 14.	
793104	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 236 of SEQ ID NO:191, b is an integer of 15 to 250, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to a + 14.	
793445	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1888 of SEQ ID NO:192, b is an integer of 15 to 1902, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to a + 14.	AA034998, AA044249, AA088830, AA429418
793446	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 546 of SEQ ID NO:193, b is an integer of 15 to 560, where both a and b correspond to the positions of	TS7765, T60664, H01264, H45774, H54790, H54842, H64484, H64485, N98810, W58332, W58653, W74582, W79320, W79420, W79565, W92452, AA027210, AA027209, AA029725, AA029663, AA088693, AA121506, AA127731, AA428362

	nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to a + 14.	
793639	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 576 of SEQ ID NO:194, b is an integer of 15 to 590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:194, and where b is greater than or equal to a + 14.	N69881, N93023, N98853, W21375, W73944, W77988, AA169530, AA169837, AA176453, AA176931
794213	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 677 of SEQ ID NO:195, b is an integer of 15 to 691, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to a + 14.	N53897, N55318
795858	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1758 of SEQ ID NO:196, b is an integer of 15 to 1772, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14.	
795955	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 661 of SEQ ID NO:197, b is an integer of 15 to 675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14.	
796359	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 543 of SEQ ID NO:198, b is an integer of 15 to 557, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to $a + 14$ .	
796555	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2597 of SEQ ID NO:199, b is an integer of 15 to 2611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to $a + 14$ .	T69136, T69194, T95612, T95713, R53091, R73126, N41876, N49174, W05348, W04725, W31397, W31827, W92674, AA039513
796675	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2302 of SEQ ID NO:200, b is an integer of 15 to 2316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:200, and where b is greater than or equal to $a + 14$ .	
796743	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1133 of SEQ ID NO:201, b is an integer of 15 to 1147, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to $a + 14$ .	
796792	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 674 of SEQ ID NO:202, b is an integer of 15 to 688, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to $a + 14$ .	
799668	Preferably excluded from the present invention are one or more	



	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 290 of SEQ ID NO:203, b is an integer of 15 to 304, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14.	
799669	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 403 of SEQ ID NO:204, b is an integer of 15 to 417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14.	
799673	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 537 of SEQ ID NO:205, b is an integer of 15 to 551, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14.	
799674	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:206, b is an integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14.	
799678	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:207, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or	

	equal to $a + 14$ .	
799728	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 255 of SEQ ID NO:208, $b$ is an integer of 15 to 269, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where $b$ is greater than or equal to $a + 14$ .	
799748	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 720 of SEQ ID NO:209, $b$ is an integer of 15 to 734, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where $b$ is greater than or equal to $a + 14$ .	H19497, H19579, H50117, H50164, H52826, H52827, H61184, H62087, H96290, H96291, N20586, N21261, N28978, N30137, N30490, N35750, W31933, W37535, N90542, AA418545, AA418511
799760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 644 of SEQ ID NO:210, $b$ is an integer of 15 to 658, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where $b$ is greater than or equal to $a + 14$ .	
799805	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 190 of SEQ ID NO:211, $b$ is an integer of 15 to 204, where both $a$ and $b$ correspond to the positions of nucleotide residues shown in SEQ ID NO:211, and where $b$ is greater than or equal to $a + 14$ .	
800296	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$ , where $a$ is any integer between 1 to 1257 of SEQ ID NO:212, $b$ is an integer of 15 to 1271, where both	

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14.	
800327	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1011 of SEQ ID NO:213, b is an integer of 15 to 1025, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14.	
800816	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 337 of SEQ ID NO:214, b is an integer of 15 to 351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14.	
800835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1073 of SEQ ID NO:215, b is an integer of 15 to 1087, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14.	
805429	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1963 of SEQ ID NO:216, b is an integer of 15 to 1977, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14.	
805458	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	T82438, T82439, R19121, R20391, R28602, R36743, R43508, R46035, R43508, R46035, R79588, H24625, N28372, N28785, N29421, N35476, N57353, N72836, N79096, W03034,

	formula of a-b, where a is any integer between 1 to 2801 of SEQ ID NO:217, b is an integer of 15 to 2815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14.	AA016073, AA019733, AA021030, AA062895, AA081968, AA115692, AA133511, AA151852, AA149707, AA194903, AA194902
805478	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1631 of SEQ ID NO:218, b is an integer of 15 to 1645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:218, and where b is greater than or equal to a + 14.	
805805	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:219, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:219, and where b is greater than or equal to a + 14.	
806486	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 818 of SEQ ID NO:220, b is an integer of 15 to 832, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:220, and where b is greater than or equal to a + 14.	
806498	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1878 of SEQ ID NO:221, b is an integer of 15 to 1892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:221, and where b is greater than or equal to a + 14.	
806819	Preferably excluded from the present	

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 854 of SEQ ID NO:222, b is an integer of 15 to 868, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:222, and where b is greater than or equal to a + 14.	
810870	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1502 of SEQ ID NO:223, b is an integer of 15 to 1516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:223, and where b is greater than or equal to a + 14.	R50267, R50730, H27672, H27673, H30138, H99256, N74342, N80868, W05054, W07601
811730	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1292 of SEQ ID NO:224, b is an integer of 15 to 1306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:224, and where b is greater than or equal to a + 14.	
813025	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 570 of SEQ ID NO:225, b is an integer of 15 to 584, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:225, and where b is greater than or equal to a + 14.	
813233	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 509 of SEQ ID NO:226, b is an integer of 15 to 523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:226, and where b is greater than or equal to a + 14.	
813262	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2363 of SEQ ID NO:227, b is an integer of 15 to 2377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:227, and where b is greater than or equal to a + 14.	
815637	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 449 of SEQ ID NO:228, b is an integer of 15 to 463, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:228, and where b is greater than or equal to a + 14.	
815853	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1218 of SEQ ID NO:229, b is an integer of 15 to 1232, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:229, and where b is greater than or equal to a + 14.	R53293, R59708, R59818, R88929, R89609, H78819, N52182, AA125808, AA128281
815999	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:230, b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:230, and where b is greater than or equal to a + 14.	
823427	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:231,	T53986, T60846, T72425, R18752, H22479, H50211, N40817, N93431, W21474, W21308, W32281, W44860, W95821, N90881, AA132037, AA131965, AA151157, AA155868, AA156600, AA156837, AA157061, AA157045, AA160623, AA169460, AA176447, AA178894,

	b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:231, and where b is greater than or equal to a + 14.	AA179764, AA180438, AA181145, AA181144, AA196382, AA196478
823704	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1460 of SEQ ID NO:232, b is an integer of 15 to 1474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:232, and where b is greater than or equal to a + 14.	
824798	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1768 of SEQ ID NO:233, b is an integer of 15 to 1782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:233, and where b is greater than or equal to a + 14.	
825018	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2194 of SEQ ID NO:234, b is an integer of 15 to 2208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:234, and where b is greater than or equal to a + 14.	
825076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2566 of SEQ ID NO:235, b is an integer of 15 to 2580, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:235, and where b is greater than or equal to a + 14.	
825787	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide	

	sequence described by the general formula of a-b, where a is any integer between 1 to 2994 of SEQ ID NO:236, b is an integer of 15 to 3008, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:236, and where b is greater than or equal to a + 14.	
826116	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 863 of SEQ ID NO:237, b is an integer of 15 to 877, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:237, and where b is greater than or equal to a + 14.	
826147	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3025 of SEQ ID NO:238, b is an integer of 15 to 3039, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:238, and where b is greater than or equal to a + 14.	
827020	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1978 of SEQ ID NO:239, b is an integer of 15 to 1992, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:239, and where b is greater than or equal to a + 14.	
827586	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 483 of SEQ ID NO:240, b is an integer of 15 to 497, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:240, and where b is greater than or equal to a + 14.	



827732	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 302 of SEQ ID NO:241, b is an integer of 15 to 316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:241, and where b is greater than or equal to a + 14.	
827735	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 815 of SEQ ID NO:242, b is an integer of 15 to 829, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:242, and where b is greater than or equal to a + 14.	
827740	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:243, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:243, and where b is greater than or equal to a + 14.	R21513, R22316, R42033, R43706, R42033, R43706, R63113, R70954, R71006, N48618, N53377, AA912400
827808	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2839 of SEQ ID NO:244, b is an integer of 15 to 2853, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:244, and where b is greater than or equal to a + 14.	
828251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1183 of SEQ ID NO:245, b is an integer of 15 to 1197, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:245, and where b is greater than or equal to a + 14.	
828357	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 834 of SEQ ID NO:246, b is an integer of 15 to 848, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:246, and where b is greater than or equal to a + 14.	
828449	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:247, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:247, and where b is greater than or equal to a + 14.	
828612	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1062 of SEQ ID NO:248, b is an integer of 15 to 1076, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:248, and where b is greater than or equal to a + 14.	R28513, R28661, R31336, R41867, R41867, R60004, H19945, H19946, H22061, H46271, H46342, H82619, H82618, N20678, W96169, AA010842, AA278855, AA582295, AA583721, AA639735, AA579409, AA568321, AA833752, AA907437, AI054389, W22584
828647	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2411 of SEQ ID NO:249, b is an integer of 15 to 2425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:249, and where b is greater than or equal to a + 14.	
828698	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 1394 of SEQ ID NO:250, b is an integer of 15 to 1408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:250, and where b is greater than or equal to a + 14.	
828962	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 480 of SEQ ID NO:251, b is an integer of 15 to 494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:251, and where b is greater than or equal to a + 14.	
828982	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2477 of SEQ ID NO:252, b is an integer of 15 to 2491, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:252, and where b is greater than or equal to a + 14.	T64550, T65973, T94849, T94894, R07359, R07409, R34782, R35670, R35781, R56137, R56532, R64039, R66397, R67131, H01215, H02256, H02354, H03227, H04019, R94572, R94573, H51242, H60286, H65939, H72416, H72857, N22537, N24628, N24936, N33813, N35712, N35830, N35916, N43982, N51363, N64462, N70838, N75470, N75760, W01444, W05279, W57605, W58752, W72612, W72970, W73260, W73535, W76678, W76207, W94918, W91971, W92319, W92355, AA024690, AA024643, AA028083, AA028084, AA028169, AA035743, AA045830, AA045917, AA081723, AA086310, AA085740, AA102651, AA101305, AA126788, AA126837, AA126865, AA127295, AA129688, AA129664, AA133503, AA133504, AA132801, AA134537, AA134547, AA186712, AA188264, AA215597, AA463977, AA464112, AA417286, AA417312, AA259228, AA279952, AA287814, AA468227, AA468302, AA526480, AA553703, AA587072, AA635683, AA639361, AA573471, AA579754, AA579812, AA580600, AA730425, AA741436, AA804629, AA829189, AA830255, AA865594, AA885821, AA918979, AA962033, AA985542, AA985571, AA987607, AA995783, AI075334, D79160, N84712, N88655, C03235, AA094028
829282	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:253, b is an integer of 15 to 1125, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:253, and where b is greater than or equal to a + 14.	
829368	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:254, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:254, and where b is greater than or equal to a + 14.	R61547, R76124, H01565, H02950, H04248, H29996, H99672, W19970
829751	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:255, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:255, and where b is greater than or equal to a + 14.	
829773	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1219 of SEQ ID NO:256, b is an integer of 15 to 1233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:256, and where b is greater than or equal to a + 14.	T96982, T97094, H53488, H53861, H64894, H65486, N62304, N67480, N78709, W03409, W07598, W73770, AA025496, AA025812, AA133948
829934	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2390 of SEQ ID NO:257, b is an integer of 15 to 2404, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:257, and where b is greater than or equal to a + 14.	
829942	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	T64541, T65964, R01423, R01424, R05277, R19450, R44699, R51779, R51780, R44699, H11322, H11349, H13859, H13911, H21393, H21437, H21890, H22117, H45982, H46047, H47137, R98886, H54491, H54854, H98744,

	between 1 to 2078 of SEQ ID NO:258, b is an integer of 15 to 2092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:258, and where b is greater than or equal to a + 14.	N23465, N37080, N46155, N46396, N58995, N62715, N93640, W60228, W60227, W74349, W76544, W87768, W87883, W90517, W90518, AA010775, AA011055, AA029083, AA029084, AA036822, AA057660, AA075916, AA082814, AA101057, AA130702, AA132788, AA133063, AA147813, AA148063, AA151487, AA151511, AA173298, AA173348, AA181036, AA187993, AA187994, AA192370, AA192357, AA243010, AA243264, AA250948
829951	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 373 of SEQ ID NO:259, b is an integer of 15 to 387, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:259, and where b is greater than or equal to a + 14.	
830173	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3698 of SEQ ID NO:260, b is an integer of 15 to 3712, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:260, and where b is greater than or equal to a + 14.	T52493, T52572, T56913, T61268, T61320, T70063, T70130, T72005, T87844, T94182, T70248, R24534, R24639, R31200, R64161, R64274, R70751, R70750, H16189, H89274, H99749, N25430, N25537, N32578, N32816, N34120, N34134, N34491, N35081, N42260, N43821, N62152, N62798, N64065, N64169, N67362, N69808, N74678, N93912, N49165, W04704, W05040, W16565, W19920, W31806, W31907, W37354, W37355, W40493, W45266, W45455, W52925, W58628, W92222, W92345, N91265, AA027083, AA027124, AA028969, AA029137, AA029257, AA083657, AA084297, AA121151, AA121131, AA126957, AA127166, AA128353, AA128495, AA128834, AA132690, AA132783, AA136553, AA152414, AA150706, AA150808, AA156272, AA164766, AA164767, AA171427, AA171794, AA173592, AA173949, AA190421, AA190580, AA191383, AA224415, AA232135
830200	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 883 of SEQ ID NO:261, b is an integer of 15 to 897, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:261, and where b is greater than or equal to a + 14.	AA524284, AA662477, AA887924

830365	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1891 of SEQ ID NO:262, b is an integer of 15 to 1905, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:262, and where b is greater than or equal to a + 14.	R42905, R59718, R62419, R72182, R72228, H22520, H22519, H25889, H45643, H46451, H46992, H84483, N50834, N92573, AA022699, AA022791, AA037734, AA037735, AA040585, AA040557, AA047816, AA159187, AA159282, AA223337, AA505391, AA515591, AA524466, AA613383, AA627298, AA578816, AA769153, AA826456, AA830896, AA831083, AA837917, AA977053, AI083822, AI090301, AI084104
830456	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1410 of SEQ ID NO:263, b is an integer of 15 to 1424, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:263, and where b is greater than or equal to a + 14.	T39800, T39875, T40331, T80148, R01135, R05754, R12866, R15287, R21703, R39361, H00652, H00741, H05366, H17706, H23423, R97800, R97849, N25478, N41797, N48511, N98906, W19893, W23945, W35174, W60540, W78229, W79282, W84685, AA022952, AA026821, AA026953, AA074956, AA075111, AA114974, AA114988, AA192860, AA193064
830549	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1273 of SEQ ID NO:264, b is an integer of 15 to 1287, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:264, and where b is greater than or equal to a + 14.	R60171, H26796, H96303, N91699, W25137, AA069218, AA088565, AA161178
830602	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 977 of SEQ ID NO:265, b is an integer of 15 to 991, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:265, and where b is greater than or equal to a + 14.	
830610	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2306 of SEQ ID NO:266, b is an integer of 15 to 2320, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:266, and where b is greater than or equal to a + 14.	
830644	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:267, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:267, and where b is greater than or equal to a + 14.	
830707	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1832 of SEQ ID NO:268, b is an integer of 15 to 1846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:268, and where b is greater than or equal to a + 14.	
830709	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 587 of SEQ ID NO:269, b is an integer of 15 to 601, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:269, and where b is greater than or equal to a + 14.	
830733	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 866 of SEQ ID NO:270, b is an integer of 15 to 880, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:270, and where b is greater than or equal to a + 14.	T26638, R49962, H96664, N71762, N90691, AA040156, AA128271, AA418045, AA418216, AA535799, AA583405, AA768811
830768	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 2470 of SEQ ID NO:271, b is an integer of 15 to 2484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:271, and where b is greater than or equal to a + 14.	
830855	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO:272, b is an integer of 15 to 751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:272, and where b is greater than or equal to a + 14.	H17127, AA100311, AA112910, AA282249, AA578649, AA748590
830949	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3295 of SEQ ID NO:273, b is an integer of 15 to 3309, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:273, and where b is greater than or equal to a + 14.	
830965	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 829 of SEQ ID NO:274, b is an integer of 15 to 843, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:274, and where b is greater than or equal to a + 14.	
830973	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2014 of SEQ ID NO:275, b is an integer of 15 to 2028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:275, and where b is greater than or equal to a + 14.	
830979	Preferably excluded from the present invention are one or more	



	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1441 of SEQ ID NO:276, b is an integer of 15 to 1455, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:276, and where b is greater than or equal to a + 14.	
830989	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:277, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:277, and where b is greater than or equal to a + 14.	
831134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1366 of SEQ ID NO:278, b is an integer of 15 to 1380, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:278, and where b is greater than or equal to a + 14.	
831200	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1004 of SEQ ID NO:279, b is an integer of 15 to 1018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:279, and where b is greater than or equal to a + 14.	
831260	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1178 of SEQ ID NO:280, b is an integer of 15 to 1192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:280, and where b is greater than or	R15008, R28066, R68324, H20638, N25438, N67982, N67983, N67999, N68004, N68005, N80403, N80423, N80429, N80430, AA024581, AA024582, AA024637, AA862760, AA091142

	equal to $a + 14$ .	
831531	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1741 of SEQ ID NO:281, b is an integer of 15 to 1755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:281, and where b is greater than or equal to $a + 14$ .	T66624, R16038, R26139, R26353, H15795, H16285, H21749, H21945, H22698, H23978, H52286, H52523, H60184, H60227, H68044, H81748, H81749, N46859, N47179, N51722, N51808, AA031701, AA031866, AA043760, AA043761, AA081005, AA081148, AA195519, AA470636, AA534463, AA555198, AA631348, AA721036, AA737025, AA761301, AA764993, AA765314, AA765749, AA878422, U47720, C21223
831665	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1079 of SEQ ID NO:282, b is an integer of 15 to 1093, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:282, and where b is greater than or equal to $a + 14$ .	
831724	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1542 of SEQ ID NO:283, b is an integer of 15 to 1556, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:283, and where b is greater than or equal to $a + 14$ .	R52161, N45179, N68350, N94021, W02782, W24840, W61323, AA907441
831884	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1015 of SEQ ID NO:284, b is an integer of 15 to 1029, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:284, and where b is greater than or equal to $a + 14$ .	
831897	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1569 of SEQ ID NO:285, b is an integer of 15 to 1583, where both	AA056348, AA127534

	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:285, and where b is greater than or equal to a + 14.	
831922	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:286, b is an integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:286, and where b is greater than or equal to a + 14.	
831963	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 492 of SEQ ID NO:287, b is an integer of 15 to 506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:287, and where b is greater than or equal to a + 14.	
832074	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:288, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:288, and where b is greater than or equal to a + 14.	
832266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1020 of SEQ ID NO:289, b is an integer of 15 to 1034, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:289, and where b is greater than or equal to a + 14.	T70612, T70879, H13555, H23264, R97792, R97842, N75850, W07434, W19866, N90056, AA043395, AA463232, AA463231
832309	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general	

	formula of a-b, where a is any integer between 1 to 3077 of SEQ ID NO:290, b is an integer of 15 to 3091, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:290, and where b is greater than or equal to a + 14.	
832342	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 504 of SEQ ID NO:291, b is an integer of 15 to 518, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:291, and where b is greater than or equal to a + 14.	
832351	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 484 of SEQ ID NO:292, b is an integer of 15 to 498, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:292, and where b is greater than or equal to a + 14.	
832352	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 455 of SEQ ID NO:293, b is an integer of 15 to 469, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:293, and where b is greater than or equal to a + 14.	
832434	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 654 of SEQ ID NO:294, b is an integer of 15 to 668, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:294, and where b is greater than or equal to a + 14.	
832490	Preferably excluded from the present	T86496, H24346, R84505, N26874, N98621,

	invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1386 of SEQ ID NO:295, b is an integer of 15 to 1400, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:295, and where b is greater than or equal to a + 14.	W04678, W04692, W24267, W93387, W94971, AA036953, AA136869, AA136799, AA147214, AA160413, AA535592, AA931261, AA931403, AA962726, AA992456
832573	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO:296, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:296, and where b is greater than or equal to a + 14.	
832580	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:297, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:297, and where b is greater than or equal to a + 14.	
833394	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 878 of SEQ ID NO:298, b is an integer of 15 to 892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:298, and where b is greater than or equal to a + 14.	
835355	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:299, b is an integer of 15 to 1624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	AA076638, AA916592, AI088936, AI089690

	NO:299, and where b is greater than or equal to a + 14.	
835497	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1955 of SEQ ID NO:300, b is an integer of 15 to 1969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:300, and where b is greater than or equal to a + 14.	
835728	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1868 of SEQ ID NO:301, b is an integer of 15 to 1882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:301, and where b is greater than or equal to a + 14.	
835978	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2790 of SEQ ID NO:302, b is an integer of 15 to 2804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:302, and where b is greater than or equal to a + 14.	
836091	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3845 of SEQ ID NO:303, b is an integer of 15 to 3859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:303, and where b is greater than or equal to a + 14.	R02093, R02205, R02336, R02439, R19436, R44685, R44685, R72354, H10160, H49884, H49885, N23208, N28789, N29901, N42953, N55093, N77305, N99373, W46396, W46504, AA082311, AA176281, AA176282, AA227971, AA228079, AA234964, AA234145, AA281787, AA281656, AA524468, AA551888, AA631173, AA639499, AA811344, AA830439, AA831974, AA923665, C03439, AA641655, AA091346, AA400968, AA400884
836274	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3364 of SEQ ID NO:304,	T75442, R20393, R43511, R43511, R73650, R73731, R80152, R80886, H97932, H98616, N33018, N71679, N99650, AA001053, AA001089, AA044947, AA044943, AA149057, AA464856, AA427892, AA228265, AA230021, AA482694, AA483691, AA484850, AA513037,

	b is an integer of 15 to 3378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:304, and where b is greater than or equal to a + 14.	AA516076, AA532381, AA583355, AA618566, AA577028, AA730651, AA730790, AA745667, AA829807, AA923038, AA931937, AA932867, AA934400, AA934413, AA971551, AA971743, AA972772, AA977253, AA992454, AA994794, AI089906, AI094921, D79281, C06099, D44840, C20741, AA283186, AA292346, AA394164
836731	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1000 of SEQ ID NO:305, b is an integer of 15 to 1014, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:305, and where b is greater than or equal to a + 14.	
838014	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2113 of SEQ ID NO:306, b is an integer of 15 to 2127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:306, and where b is greater than or equal to a + 14.	
838874	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 652 of SEQ ID NO:307, b is an integer of 15 to 666, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:307, and where b is greater than or equal to a + 14.	R61165, N44200
839120	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2157 of SEQ ID NO:308, b is an integer of 15 to 2171, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:308, and where b is greater than or equal to a + 14.	T74462, R18264, H23432, AA279685, AA847441, AA904076, AA393782

839611	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 6149 of SEQ ID NO:309, b is an integer of 15 to 6163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:309, and where b is greater than or equal to a + 14.	T93695, T93696, T96161, R32227, R32254, R32304, R33503, R34044, R71178, H93366, N50709, N55039, AA165143, AA199856, AA199927, AA234331, AA262892, AA423987, AA423986, AA525886, AA661602, AA731504, AA741228, AA814795, AA828858, AA829196, AA831198, AA834822, AA865590, AA886436, AA903649, D82270, D82453, D82464, AA642466, AA219620, AA219628, AA400707, AA400674, AA421941, AA633988, AA663219, AA663250, AA665538, AA724260, AI074714, T26891, T26926
840138	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2072 of SEQ ID NO:310, b is an integer of 15 to 2086, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:310, and where b is greater than or equal to a + 14.	
840616	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2149 of SEQ ID NO:311, b is an integer of 15 to 2163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:311, and where b is greater than or equal to a + 14.	
840780	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1383 of SEQ ID NO:312, b is an integer of 15 to 1397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:312, and where b is greater than or equal to a + 14.	
840857	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4092 of SEQ ID NO:313, b is an integer of 15 to 4106, where both	T50389, T50520, T55419, T55495, T55974, T57220, R34591, R34592, R69726, H21148, R85777, R99233, H61311, H62351, H85185, H88299, N23288, N32662, N58504, N78093, N92665, N99611, AA005068, AA007333, AA007334, AA036884, AA044715, AA045458, AA046500, AA045654, AA115936, AA121004,



	a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:313, and where b is greater than or equal to a + 14.	AA126775, AA133605, AA133606, AA133980, AA181633, AA182611, AA232979, AA233365, AA459953, AA460042, AA282826, AA285050, AA506082, AA558006, AA601060, AA767799, AA804323, AA807029, AA807087, AA825536, AA833810, AA922732, AA928638, AA960990, N56482, N62047, W27456, W26569, AA092778, AA652535, AA065256, AA065257, AA450197, AA452846, AA452986, AA705224, Z19460, AA884767, AA969488, AA977494, AI002996, AI032008, Z28526, D20112, T19336
840862	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:314, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:314, and where b is greater than or equal to a + 14.	T94528, N40545, N46592, N92934, AA570273, AA873604, AA910827, AA932397, AA971868, AI095210, N56229, AA648290, F20835, AA629912
840864	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1924 of SEQ ID NO:315, b is an integer of 15 to 1938, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:315, and where b is greater than or equal to a + 14.	R40870, R44820, H26640, W78814, W80713, AA195492, AA937549, AI085492, AI094865, AA449317, AA884600, AA909529, AA923452, AA971781, AI084795, AI089007, AA702758, AA702769
840936	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 804 of SEQ ID NO:316, b is an integer of 15 to 818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:316, and where b is greater than or equal to a + 14.	
840938	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 823 of SEQ ID NO:317, b is an integer of 15 to 837, where both a and b correspond to the positions of	

	nucleotide residues shown in SEQ ID NO:317, and where b is greater than or equal to a + 14.	
841884	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1434 of SEQ ID NO:318, b is an integer of 15 to 1448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:318, and where b is greater than or equal to a + 14.	
842241	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1479 of SEQ ID NO:319, b is an integer of 15 to 1493, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:319, and where b is greater than or equal to a + 14.	
843712	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 595 of SEQ ID NO:320, b is an integer of 15 to 609, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:320, and where b is greater than or equal to a + 14.	R02291, N94598, W85882, AA255975
844040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 488 of SEQ ID NO:321, b is an integer of 15 to 502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:321, and where b is greater than or equal to a + 14.	W24428, AA143434, AA459809
844336	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer	

	between 1 to 2616 of SEQ ID NO:322, b is an integer of 15 to 2630, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:322, and where b is greater than or equal to a + 14.	
844612	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1860 of SEQ ID NO:323, b is an integer of 15 to 1874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:323, and where b is greater than or equal to a + 14.	
844617	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2311 of SEQ ID NO:324, b is an integer of 15 to 2325, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:324, and where b is greater than or equal to a + 14.	
845251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:325, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:325, and where b is greater than or equal to a + 14.	T68474, AA159183, AA464447, AA424290, AA424487, AA631793, AA928390, AA946921, AA975194, AA977141, AA430527, AA430612, AA477798
845764	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 230 of SEQ ID NO:326, b is an integer of 15 to 244, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:326, and where b is greater than or equal to a + 14.	
846187	Preferably excluded from the present invention are one or more	

	<p>polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2440 of SEQ ID NO:327, b is an integer of 15 to 2454, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:327, and where b is greater than or equal to a + 14.</p>	
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#### *Polynucleotide and Polypeptide Variants*

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, and/or the cDNA sequence contained in a cDNA clone contained in the deposit.

5 The present invention also encompasses variants of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

10 "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 15 97%, 98%, 99% or 100%, identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the related cDNA contained in a deposited library or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide 20 sequence encoding the polypeptide encoded by the cDNA in the related cDNA contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polypeptides encoded by these nucleic acid molecules are also encompassed by the invention. In another embodiment, the invention encompasses nucleic acid molecules which comprise or alternatively consist of, a 25 polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under low stringency conditions, to the nucleotide coding sequence in SEQ ID NO:X, the

nucleotide coding sequence of the related cDNA clone contained in a deposited library, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these polypeptides under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be, for example, an entire sequence referred to in Table I, an ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of

the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases

were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence in SEQ ID NO:Y or a fragment thereof, the amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237- 245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window

Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results.

5 This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject  
10 residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues  
15 to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue  
20 query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the  
25 FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected.  
30 Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the



purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, as discussed herein, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem.* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that

"[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

5 Furthermore, as discussed herein, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are  
10 removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptide of the invention of which they are a  
15 variant. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein or fragments thereof, (e.g., including but not limited to fragments encoding a polypeptide  
20 having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid  
25 molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot  
30 analysis for detecting mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed

herein, which do, in fact, encode a polypeptide having a functional activity of a polypeptide of the invention.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA in the related cDNA clone contained in a deposited library, the nucleic acid sequence referred to in Table 1 (SEQ ID NO:X), or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells,

Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30

amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein), an amino acid sequence encoded by SEQ ID NO:X or fragments thereof, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or fragments thereof, is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

#### *Polynucleotide and Polypeptide Fragments*

The present invention is also directed to polynucleotide fragments of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers, for example, to a polynucleotide having a nucleic acid sequence which: is a portion of the cDNA contained in a deposited cDNA clone; or is a portion of a polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited cDNA clone; or is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; or is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; or is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, at least about 100 nt, at least about 125 nt or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from, for example, the sequence contained in the cDNA in a related cDNA clone contained in a deposited library, the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides. These nucleotide fragments have uses that

include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 150, 175, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the polynucleotide of which the sequence is a portion. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from

about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of the cDNA nucleotide sequence contained in the deposited cDNA clone, or the complementary strand thereto. In this context "about" includes the particularly recited range, or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the cDNA nucleotide sequence contained in the deposited cDNA clone. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, and/or encoded by the cDNA contained in the related cDNA clone contained in a deposited library. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region.

Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, an amino acid sequence from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, 1441-1460, 1461-1480, 1481-1500, 1501-1520, 1521-1540, 1541-1560, 1561-1580, 1581-1600, 1601-1620, 1621-1640, 1641-1660, 1661-1680, 1681-1700, 1701-1720, 1721-1740, 1741-1760, 1761-1780, 1781-1800, 1801-1820, 1821-1840, 1841-1860, 1861-1880, 1881-1900, 1901-1920, 1921-1940, 1941-1960, 1961-1980, and 1981 to the end of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.



Accordingly, polypeptide fragments of the invention include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in the related cDNA clone contained in a deposited library). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed

herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in deposited cDNA clone referenced in Table I). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and  
5 where n corresponds to the position of an amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides  
10 having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y), and/or the cDNA in the related cDNA clone contained in a deposited library, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also  
15 encompassed by the invention.

Any polypeptide sequence contained in the polypeptide of SEQ ID NO:Y, encoded by the polynucleotide sequences set forth as SEQ ID NO:X, or encoded by the cDNA in the related cDNA clone contained in a deposited library may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide  
20 encoded by a polynucleotide sequence of SEQ ID NO:X, or the cDNA in a deposited cDNA clone may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions,  
25 turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that  
30 combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Preferred polypeptide fragments of the invention are fragments comprising, or alternatively consisting of, an amino acid sequence that displays a functional activity of the polypeptide sequence of which the amino acid sequence is a fragment.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Table 4

Sequence/ Contig ID	Epitope
508678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 422 as residues: Gln-21 to Arg-43.
508968	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 423 as residues: Thr-1 to Lys-6.
509029	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 424 as residues: Asp-1 to Trp-8, Thr-12 to Cys-19, Pro-41 to Leu-51.
522632	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 426 as residues: Cys-69 to Asn-74, Lys-83 to Gly-89.
524655	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 427 as residues: Tyr-28 to Asn-35, Ile-45 to Lys-55.
525847	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 428 as residues: Lys-27 to Asp-33.
530306	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 429 as residues: Arg-1 to Arg-11, Tyr-21 to His-27.
532818	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 430 as residues: Pro-10 to Thr-21, Asp-32 to Thr-38, Gly-47 to Glu-60.
533385	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 431 as residues: Asn-17 to Trp-22, Pro-34 to Glu-49, His-61 to Ser-71.
533532	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 432 as residues: Glu-29 to Lys-37, Lys-110 to Ile-118, Arg-126 to Cys-135, Lys-157 to Gly-163, Gln-188 to Trp-201, Glu-269 to Thr-278.
534852	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 433 as residues: Gln-1 to Ser-14, Thr-23 to Val-31, Cys-43 to Ala-56, Glu-58 to Ser-96, Gly-101 to Tyr-109, Asn-143 to Tyr-148, Pro-154 to His-164, Ser-195 to Asn-201, Pro-264 to Pro-271.
537910	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 434 as residues: Pro-4 to Ala-11, Pro-110 to Arg-122.
539577	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 436 as residues: Pro-9 to Gln-19.
548595	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 439 as residues: Asp-27 to Asp-33, His-54 to Tyr-59, Ile-91 to Pro-96.
549337	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 440 as residues: Pro-38 to Asp-43, Arg-155 to Phe-162, Pro-164 to Asp-170, Pro-172 to Gly-182.
553091	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 442 as residues: Lys-55 to Lys-62, Gln-67 to Val-76, Lys-101 to Glu-111, Lys-125 to Arg-140, Arg-161 to Arg-166, Gln-171 to Asp-187.
553827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 443 as residues: Glu-17 to Pro-22, Pro-70 to His-76, Thr-84 to Arg-92, Asp-109 to Tyr-117.
556350	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 444 as residues: Glu-1 to Ser-15, Phe-17 to Pro-22, Lys-116 to Arg-131.
556351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 445 as residues: Gln-9 to Phe-23, Cys-53 to Ser-64, Glu-86 to Asp-93, Ile-100 to Glu-112, Tyr-124 to Glu-133, Ser-197 to Ser-204, Asn-208 to Glu-214, Lys-228 to Lys-233, Tyr-248 to Lys-259, Pro-330 to Ala-335, Gln-349 to Lys-355, Ala-365 to Glu-374, Ser-376 to Ser-397.
557007	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 446 as residues: Pro-46 to Tyr-54, Pro-81 to Gly-87, Pro-97 to Gly-104, Leu-106 to Asn-116, Asn-129 to Phe-134, Lys-147 to Tyr-158, Ala-192 to Ser-199, Asp-204 to Glu-215, Gly-221 to Ser-232.
558456	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 448 as

	residues: Glu-19 to Tyr-24, Ser-60 to Thr-65, Thr-82 to Pro-88.
558708	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 449 as residues: Arg-13 to Ala-20, Pro-27 to Arg-32, Lys-37 to Glu-62.
574789	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 450 as residues: Gly-16 to Lys-21.
578203	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 451 as residues: Thr-7 to Arg-18.
588869	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 453 as residues: Pro-14 to Ser-19, Glu-55 to Phe-60, Asp-93 to Ser-98, Thr-138 to Tyr-144, Asn-155 to Phe-163, Arg-168 to Ser-175, Gln-205 to Lys-210, Phe-226 to Thr-233.
597076	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 454 as residues: Ser-50 to Gln-56.
598656	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 455 as residues: Ser-85 to Tyr-92, Arg-109 to Lys-114.
614329	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 457 as residues: Arg-59 to Ala-67, Asn-78 to Arg-85.
620956	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 459 as residues: Ala-11 to Gln-16.
621889	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 460 as residues: Ser-84 to Gly-99, Pro-101 to Ser-112.
651784	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 462 as residues: Gly-29 to Gly-35, Ala-37 to Ala-48.
651826	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 463 as residues: Arg-1 to Ser-16, Gln-49 to Lys-60, Glu-77 to Leu-83, Gln-91 to Arg-100, Phe-140 to Ala-154, Asp-214 to Leu-219, Ala-258 to Met-275, Ile-289 to Lys-295, Ala-314 to Glu-320, Arg-327 to Met-332, Thr-383 to Ser-388, Ser-425 to Asp-433.
653282	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 464 as residues: Arg-12 to Ile-19, Glu-23 to Pro-29, Pro-37 to Val-45.
657122	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 465 as residues: Ala-6 to Gly-13, Arg-41 to Thr-47.
661442	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 466 as residues: Arg-6 to Ser-11, Asp-53 to Ser-59, Ala-88 to Ala-104, Thr-114 to Asn-121, Glu-128 to Val-137, Asn-144 to Thr-150, Ser-174 to Asn-180, Gly-203 to Asp-212.
664914	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 467 as residues: Pro-12 to Lys-17.
666654	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 468 as residues: Thr-5 to Leu-10, Pro-13 to Leu-24.
667084	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 469 as residues: Pro-1 to Pro-9, Gly-50 to Ser-55, Gly-80 to Ser-85, Gly-91 to Tyr-96, Arg-144 to Gln-160, Asp-195 to Thr-202, Lys-246 to Glu-252, Met-283 to Glu-288, Glu-292 to Glu-299, Ser-304 to Asn-310, Ala-356 to Tyr-362, Met-387 to Tyr-394, Gln-424 to Thr-431, Ser-450 to Arg-459.
667380	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 470 as residues: Pro-1 to Pro-6, Thr-134 to Gln-140, Tyr-142 to Arg-150.
671315	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 472 as residues: Ala-16 to Gly-21, Glu-28 to Gly-35.
671993	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 473 as residues: Pro-8 to Ser-23.
674618	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 474 as residues: Ile-3 to Ser-11, Arg-24 to Glu-30.
675027	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 475 as residues: His-47 to Ile-52, Ala-71 to Arg-76, Asp-78 to Lys-87.
677202	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 476 as residues: Val-45 to Gly-50, Thr-56 to Glu-64.
678504	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 477 as residues: Arg-7 to Ser-19.

678985	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 478 as residues: Lys-17 to Thr-23, Leu-26 to His-36, His-41 to Pro-56, Ala-60 to Gly-71, Lys-77 to Ser-91, Asp-101 to Lys-109, Asp-200 to Gly-206, Asp-245 to Leu-253, Gln-262 to Phe-274.
682161	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 479 as residues: Arg-5 to Pro-11, Pro-22 to Thr-29, Trp-53 to Arg-62, Pro-69 to Gly-78, Lys-98 to Tyr-103, Glu-144 to His-151, Pro-172 to Leu-178, Gln-193 to Glu-200.
683476	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 480 as residues: Ala-5 to Trp-19.
693589	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 482 as residues: Cys-1 to Arg-13, Pro-15 to Gly-21, Gly-54 to Ser-59, Trp-73 to Lys-78, Ser-90 to Arg-104.
694991	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 483 as residues: Lys-1 to Thr-6, Pro-8 to Gly-19, Val-61 to Arg-66.
698669	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 485 as residues: Pro-31 to His-36, Gly-43 to Tyr-48, Glu-136 to Ser-142, Pro-178 to Arg-183, Pro-273 to Asp-278, Gly-318 to Cys-326.
707357	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 488 as residues: Gly-6 to Arg-21, Arg-89 to Asp-94.
707360	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 489 as residues: Ser-13 to Glu-26, Ser-48 to Val-55, Lys-85 to Thr-91, Asp-115 to Trp-120.
707375	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 490 as residues: Arg-1 to Gly-6, Ala-12 to Arg-19, Arg-34 to Arg-40, Arg-47 to Ala-58, Ser-67 to Thr-80, Ser-109 to Ser-117, Asn-134 to Ser-141, Pro-175 to Arg-181, Lys-212 to Thr-218, Asp-275 to Cys-285.
707754	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 491 as residues: Val-32 to Leu-41, Asn-55 to Arg-63, Pro-104 to Ala-113.
712248	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 493 as residues: Ser-13 to Gly-20, Gln-36 to Ser-41, Pro-44 to Phe-58.
715445	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 494 as residues: Gly-23 to Thr-29, Ser-32 to Val-40, Lys-181 to Ser-188, Glu-197 to Gln-204, Arg-244 to His-249, Ala-253 to Thr-264.
716362	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 495 as residues: Cys-1 to Gly-8, Arg-71 to Ser-77, His-102 to Ser-108.
716835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 496 as residues: Gln-7 to Glu-14, Ala-24 to Arg-41.
717685	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 498 as residues: Gly-1 to Ala-7, His-70 to Gly-76, Gln-130 to Thr-135, Thr-182 to Pro-189, Asn-259 to Leu-267, Glu-280 to Ala-289, Gln-303 to Asn-310.
719755	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 499 as residues: Asp-14 to Pro-25, Pro-59 to Glu-100, Cys-126 to Gly-145, Pro-158 to Lys-164, Lys-176 to Leu-197, Leu-221 to Tyr-238.
720389	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 500 as residues: Thr-13 to Ala-19, Ala-26 to Pro-36, Ser-63 to Gly-68.
720903	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 501 as residues: Asn-6 to Ser-11, Ala-91 to Arg-99, Trp-107 to Tyr-113, Tyr-131 to Met-137, Asp-150 to Val-157.
721562	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 503 as residues: Asp-39 to Ile-45.
722775	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 504 as residues: Pro-34 to Ser-41, Cys-49 to Arg-55, Thr-92 to Ala-98, Thr-160 to Gly-173, Thr-194 to Pro-200, Gly-274 to Trp-282, Pro-285 to Ala-291.
724463	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 505 as residues: Glu-9 to Lys-15, Pro-23 to Tyr-33.
728418	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 507 as residues: Ala-6 to Gln-11, Ser-25 to Ser-30, Lys-63 to Gly-69, Ser-108 to Asp-118, Arg-

	127 to His-132, Asp-156 to Cys-161.
728920	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 508 as residues: Thr-7 to Ala-15.
732958	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 509 as residues: Thr-10 to Ala-15, Pro-63 to Ser-78, Ser-82 to Leu-94.
733134	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 510 as residues: Arg-4 to Gly-24, Lys-47 to Phe-55, Lys-61 to Ala-67, Gly-108 to Thr-114, Pro-184 to Pro-191, Pro-292 to Arg-299, Pro-355 to Glu-392.
734099	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 511 as residues: His-1 to Arg-7, Gln-15 to Ala-23, Met-43 to Gln-55.
738911	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 515 as residues: Arg-4 to Asp-10, Ser-64 to His-75, Pro-127 to Asn-136, Phe-143 to Gln-150.
739226	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 516 as residues: Asn-1 to Thr-7.
739527	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 517 as residues: Gly-1 to Arg-9, Val-28 to Glv-39, Asp-52 to Leu-60, Ala-106 to Trp-117.
744331	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 520 as residues: Ser-17 to Arg-24.
744751	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 521 as residues: Ser-8 to Val-13, Pro-34 to Cys-40, Tyr-48 to Ser-55, Glv-63 to Ser-73.
745750	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 522 as residues: Ser-2 to Glu-17.
746285	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 523 as residues: Lys-87 to Lys-92.
746416	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 524 as residues: Arg-6 to Leu-12, Tyr-18 to Asp-25.
747851	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 525 as residues: Gly-124 to Ser-129, Leu-162 to Gly-167, Val-272 to Ala-278, Lys-293 to Asp-298.
751315	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 527 as residues: Cys-12 to Pro-20.
754634	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 529 as residues: Asp-1 to Thr-10.
756833	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 531 as residues: Thr-36 to Pro-49, Glu-52 to Pro-67.
756878	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 532 as residues: Pro-8 to Lys-15, Gly-69 to Trp-75.
757332	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 533 as residues: Gln-23 to Val-31, Phe-39 to Ile-52.
760835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 534 as residues: Phe-1 to Lys-7, Cys-82 to Ser-90.
761760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 535 as residues: Arg-34 to Pro-39, Gly-43 to Asp-51, Gln-147 to Arg-153.
762520	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 536 as residues: His-6 to His-11, Ala-13 to Glu-18, Ala-60 to Ser-65, Ile-72 to Ser-77, Gln-95 to Phe-101, Leu-136 to Ser-142.
764461	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 537 as residues: Val-15 to Ala-22, Val-26 to Glv-38.
764517	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 538 as residues: Gly-30 to Lys-36, Gly-94 to Ala-100, Gln-150 to Gly-156, Gln-189 to Leu-195.
765132	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 539 as residues: Asn-80 to Thr-87, Ser-165 to Leu-182, Thr-196 to His-201, Lys-271 to His-279, Asp-286 to Gly-292, Tyr-294 to Leu-302.
765667	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 540 as residues: Pro-14 to Pro-21, Pro-30 to Pro-36.

767113	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 541 as residues: Ala-62 to Pro-73, Pro-75 to Thr-83, Thr-110 to Phe-115, Glu-142 to Asp-150, Gln-158 to Ser-167, Glu-182 to Thr-187, Ser-190 to Asp-204.
767204	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 542 as residues: Ala-22 to Met-29, Arg-45 to Phe-56, Asp-63 to Asp-71, Gly-81 to Ala-88, Gln-155 to Trp-162.
767962	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 544 as residues: Glu-126 to Gly-132, Asn-146 to Ser-158, Phe-179 to Leu-188.
768040	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 545 as residues: Pro-24 to Trp-32, Val-51 to Arg-62, Gly-84 to Asp-93, Asp-108 to Asn-120, Glu-150 to Val-158, Gly-169 to Gly-175.
769956	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 546 as residues: Pro-1 to Arg-6.
770133	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 547 as residues: Glu-1 to Ser-6.
771964	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 549 as residues: Pro-8 to Gly-15, Thr-26 to Phe-32, Thr-102 to Ser-109, Ala-112 to Thr-118, His-130 to Glu-152, Ser-161 to Ala-170, Ser-204 to His-209, Gly-221 to Ser-229, Ser-233 to Ala-240, Glu-242 to Pro-247, Leu-251 to Gln-258, Leu-278 to Leu-285, Thr-333 to Glu-338.
773387	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 551 as residues: Lys-36 to Lys-45, Ala-59 to Arg-67, Cys-99 to Arg-108, Ala-115 to Cys-125, Arg-143 to Arg-153.
773827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 552 as residues: Pro-1 to Ala-15, Ser-72 to His-79, Gly-89 to Tyr-105, Lys-179 to Lys-184, Arg-246 to Asp-251, Glu-302 to Lys-309, Ser-329 to Phe-341.
774108	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 553 as residues: Ala-1 to Gly-21, Pro-28 to Leu-39, Pro-48 to Asp-62, Arg-71 to Arg-78.
775339	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 555 as residues: Asp-6 to Thr-13, Asp-24 to Met-30.
775582	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 556 as residues: Gly-1 to Asn-12, Ser-69 to Glu-77.
777809	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 558 as residues: Arg-15 to Gly-25.
778927	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 559 as residues: Ala-74 to Ser-82, Asn-109 to Ala-124, Ser-147 to Ile-152, Pro-188 to Gly-194, Arg-290 to Pro-299, Tyr-307 to Glu-319, Tyr-341 to Ile-346, Lys-423 to Ser-441, Gln-452 to Glu-465.
779262	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 560 as residues: Arg-5 to Ile-24, Gly-35 to Trp-40, Glu-42 to Thr-48, Lys-76 to Gly-95.
780149	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 562 as residues: Gly-13 to Gln-18, Pro-71 to Glu-89, Ile-134 to Asp-139, Pro-232 to Met-240.
780583	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 563 as residues: Asn-58 to Thr-64, Ile-72 to Ser-78, Gly-119 to Lys-128.
780960	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 564 as residues: Ala-7 to Ile-14, Lys-27 to Asp-35, Thr-63 to Leu-73.
781469	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 565 as residues: Pro-1 to Ala-12, Arg-27 to Gln-45, Arg-57 to Gln-64, Lys-74 to Asp-96.
781771	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 567 as residues: Glu-38 to Leu-52, Glu-64 to Lys-72, Asn-92 to Ala-102, Ala-104 to Asp-119, Pro-121 to Pro-130, Ser-165 to Ser-173.
782033	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 568 as residues: Ala-1 to Gly-19, Gln-41 to Gly-46.
782105	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 569 as residues: Leu-13 to Gly-34, Arg-77 to Pro-85, Lys-129 to Arg-135.
782122	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 570 as



	residues: Pro-1 to Arg-6, Ala-102 to Ala-108, Pro-148 to Asp-158, Gly-164 to Ala-171, Pro-223 to Asn-231, Pro-272 to Ser-282, Ala-294 to Pro-310, Pro-322 to Arg-327.
783245	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 572 as residues: Leu-90 to Arg-97, Ala-107 to Pro-113.
783247	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 573 as residues: Ser-2 to Leu-8.
783413	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 574 as residues: Lys-33 to Val-39.
784407	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 575 as residues: Gly-28 to Val-36.
784548	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 576 as residues: Trp-1 to Pro-9, Pro-15 to Gln-24, Pro-52 to Thr-57.
785677	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 578 as residues: Gly-7 to Gly-14.
786238	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 579 as residues: Gly-1 to Gly-8.
786389	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 580 as residues: Ser-2 to Arg-16, Gly-34 to Glu-44, Arg-62 to Gln-69, Pro-102 to Ile-108, Asp-187 to Thr-193, Leu-203 to Pro-213.
786929	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 581 as residues: Pro-2 to Trp-7, Tyr-36 to Tyr-43.
786932	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 582 as residues: Ser-18 to His-30, Thr-39 to Arg-51, Leu-59 to Thr-66, Pro-131 to Lys-136, Pro-149 to Ser-157.
787078	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 583 as residues: Glu-20 to Pro-26.
787283	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 585 as residues: Glu-7 to Arg-13, Gln-26 to Arg-34.
788988	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 587 as residues: Pro-41 to Tyr-50, Thr-70 to Lys-75.
789092	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 588 as residues: Thr-27 to Ala-34, Leu-41 to Glu-48, Glu-76 to Asn-87, Asn-110 to Leu-118, Gly-125 to Lys-133.
789298	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 589 as residues: Arg-1 to Ser-14, Glu-56 to Gly-61, Ala-92 to Gln-98, Glu-134 to Val-154.
789718	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 591 as residues: Cys-17 to Ala-24.
790285	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 594 as residues: Thr-11 to Leu-18, Leu-22 to Val-31, Trp-33 to Lys-49, Ser-63 to Glu-72, Cys-80 to Ala-91, Pro-97 to His-116.
790509	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 595 as residues: Ser-6 to His-20, Leu-22 to Gly-32, Lys-103 to Arg-111, Ser-125 to Gly-130, Glu-204 to His-210, Thr-213 to His-219, Pro-222 to Asp-244, Ser-250 to Glu-258, Arg-263 to Arg-268.
790775	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 596 as residues: Arg-42 to Asp-48, Cys-79 to Thr-85, Leu-113 to Ser-123.
790888	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 597 as residues: Pro-14 to Asp-19, Asp-40 to Leu-45, Ser-53 to Val-58, Leu-81 to Tyr-91.
791506	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 598 as residues: Arg-1 to Gly-9, Asp-19 to His-25, Gly-51 to Glu-61.
792002	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 601 as residues: Arg-1 to Gly-6, Val-22 to Pro-35, Val-106 to Ile-112, His-118 to Gln-124, Ser-132 to Leu-145, Asn-164 to Asn-170, Arg-187 to Tyr-192.
792291	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 602 as residues: Pro-14 to Arg-31.
792371	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 603 as

	residues: Gly-37 to Gly-52, Pro-63 to Gly-69, Ser-74 to His-81, Ser-94 to Thr-105, Val-109 to Thr-114, Phe-165 to Ser-181, Ala-191 to Asp-196, Asn-209 to Ser-216.
792660	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 604 as residues: Thr-11 to Arg-16, Asn-78 to Asp-84.
792782	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 605 as residues: Ala-65 to Glv-81.
792890	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 606 as residues: Pro-26 to His-31, Arg-34 to Ser-44, Pro-59 to Ser-71, Leu-77 to Gly-83.
792931	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 607 as residues: Pro-3 to His-12.
792943	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 608 as residues: Lys-3 to Tyr-9, Gly-15 to Thr-22, Leu-36 to Asp-41, Leu-67 to Lys-76, Asp-86 to Ser-93, Tyr-174 to Asp-184, Leu-255 to Glu-260, Ile-331 to Val-337.
793446	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 611 as residues: His-1 to Gly-12.
793639	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 612 as residues: Arg-6 to Arg-13, Pro-47 to Val-52, Gln-57 to Arg-65, Arg-72 to Glu-78, Asp-117 to Thr-124, Phe-132 to His-137.
794213	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 613 as residues: Tyr-1 to Trp-9, Thr-44 to Leu-49.
795955	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 615 as residues: Lys-60 to Lys-65, Lys-99 to Ala-104.
796555	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 617 as residues: Ser-1 to Gly-10, Glv-90 to Gly-97, Asn-185 to Arg-197, Pro-202 to Arg-211.
796675	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 618 as residues: Ser-35 to Gly-40, Ser-103 to His-109, Tyr-151 to Gly-159, Pro-216 to Glu-224, Asn-249 to Trp-258, Pro-278 to Glu-284.
796743	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 619 as residues: Asn-1 to Gly-6, Asn-100 to Glu-106, Gln-108 to Asp-116, Asp-146 to Thr-151, Thr-191 to Glu-198.
796792	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 620 as residues: Asn-23 to Gly-28, Cys-41 to Asp-47, Gln-82 to Glu-88.
799668	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 621 as residues: Gly-2 to Arg-10, Ile-27 to Pro-33.
799669	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 622 as residues: Gly-1 to Ser-12.
799673	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 623 as residues: Gly-1 to Ala-14, Leu-38 to Pro-46.
799674	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 624 as residues: Pro-39 to Pro-45.
799678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 625 as residues: Lys-54 to Ser-60, Tyr-86 to His-93.
799728	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 626 as residues: Trp-7 to Gln-19.
799748	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 627 as residues: Glu-7 to Arg-12, Lys-62 to His-68.
799760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 628 as residues: Ile-15 to Trp-22.
800296	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 630 as residues: Asn-19 to Thr-39, Glu-42 to Ile-48, Arg-55 to Asp-66, Ile-130 to Arg-135, Lys-149 to Ala-156, Glu-166 to Leu-176, Met-213 to Lys-219, Pro-233 to Pro-248, Lys-258 to Lys-263.
800327	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 631 as residues: Arg-13 to Gly-19, Lys-32 to Glu-39, Lys-94 to Trp-100, Asn-102 to Asp-108, Ala-117 to Leu-129.
800816	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 632 as

	residues: Lys-1 to Ile-11, Gln-36 to Leu-46.
800835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 633 as residues: Trp-1 to Gln-11, Gly-37 to Gln-50, Ser-109 to Gln-114, Glu-146 to Leu-155, Glu-175 to Gly-180, Thr-188 to Ser-200.
805429	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 634 as residues: Pro-6 to Ser-51, Gln-100 to Glu-107.
805458	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 635 as residues: Glu-57 to Ser-62, Thr-102 to Ser-120.
805478	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 636 as residues: Glu-31 to Glu-37, Pro-47 to Ser-52, Asn-57 to Asn-66.
805805	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 637 as residues: Arg-1 to Cys-16, Tyr-59 to Lys-68, Glu-76 to Arg-82.
806486	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 638 as residues: Phe-1 to Val-6, Pro-11 to Gly-18.
806498	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 639 as residues: Pro-6 to Ser-17, Arg-81 to Thr-88, Arg-198 to Val-203, Arg-285 to Arg-296, Gln-302 to Ser-361, Leu-399 to Ser-407.
810870	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 641 as residues: Val-12 to Ile-21.
811730	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 642 as residues: Arg-33 to Arg-40.
813262	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 645 as residues: Gly-31 to Asp-51, Cys-68 to Val-81, Leu-85 to Cys-92.
815637	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 646 as residues: Arg-13 to Asp-19, Ser-80 to Gly-91, Pro-99 to Ser-111.
815853	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 647 as residues: Cys-25 to Ser-31, Gln-63 to Asp-73, Arg-98 to Gly-106, Pro-120 to Arg-125, Leu-136 to Asp-141, Gly-155 to Glu-170, Phe-179 to Gly-186.
815999	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 648 as residues: Asp-1 to Asp-10, Arg-19 to Glu-28, Gly-86 to Leu-93, Arg-113 to His-118.
823427	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 649 as residues: Pro-16 to Cys-27, Arg-70 to Arg-76.
823704	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 650 as residues: Val-29 to Lys-34, Arg-58 to His-63, Gln-87 to Lys-97, Arg-195 to Ser-200.
824798	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 651 as residues: Thr-28 to His-34.
825018	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 652 as residues: Gln-1 to Asn-11, Leu-19 to Thr-24, Lys-47 to Arg-55, Lys-94 to Asp-99, Ala-101 to Arg-107, Ala-137 to Tyr-146, Gln-150 to Ser-163, Gly-169 to Lys-175, Thr-182 to Ala-189, Glu-249 to Ser-258, Pro-266 to Tyr-275, Tyr-285 to Gly-298, Asp-302 to Gln-315, Tyr-318 to Thr-325, Gln-332 to Ala-359, Ser-372 to Phe-384, Leu-390 to Ala-399, Ala-428 to Arg-437.
825787	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 654 as residues: Pro-21 to Leu-28, Arg-40 to Ile-49, Asp-84 to Asn-93, Arg-124 to Asn-130, Gly-140 to Asn-145, Leu-187 to Gln-196, Pro-208 to Asp-213, Arg-244 to Asp-252, Ile-325 to Gln-336, Glu-372 to Ala-379, Asn-435 to Leu-446, Ala-460 to Arg-467, Val-500 to Asp-506, Lys-524 to Asn-533, Thr-592 to Lys-598, Asp-648 to Ser-656.
826116	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 655 as residues: Glu-20 to Cys-35.
826147	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 656 as residues: Lys-18 to Leu-24.
827586	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 658 as residues: Ser-7 to Gly-14, Leu-22 to Ala-28, Thr-57 to Ser-62.
827735	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 660 as residues: Pro-2 to Ser-12, Gln-25 to Glu-31, Val-40 to Arg-45.
827740	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 661 as

	residues: Ile-22 to Lys-28.
827808	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 662 as residues: Glu-2 to Gln-13, Gln-20 to Gly-29, Arg-32 to Cys-47, Pro-54 to Trp-61, Thr-73 to Gln-91, Gly-96 to Ser-103.
828357	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 664 as residues: Gly-1 to Gly-10, Val-25 to Glu-32, His-67 to Arg-73.
828612	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 666 as residues: Asp-25 to Gln-31, Asp-36 to Tyr-41, Gln-43 to Thr-48, Lys-71 to Thr-76.
828647	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 667 as residues: Ser-2 to Ser-8, Arg-61 to Gln-74, Ser-192 to Asn-202, Gln-229 to Lys-236, Gly-281 to Gly-292, Glu-333 to Ala-345, Ala-352 to Gln-358, Glu-360 to Leu-366, Asp-443 to Ser-449, Glu-452 to Glu-459, Asp-485 to Thr-492, Ala-510 to Gln-516, Ala-545 to Ala-552, Leu-560 to Thr-566, Glu-586 to Ala-592, Asp-601 to Gln-607, Leu-609 to Leu-620.
828698	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 668 as residues: Pro-28 to Ser-43, Pro-45 to Ala-50, His-58 to Gln-63.
828962	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 669 as residues: Ala-42 to Gly-49, Thr-54 to Cys-63.
829282	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 671 as residues: Ser-7 to Gln-12, Gly-25 to Gly-31, Gly-71 to Gly-84, Leu-147 to Glu-164, Trp-172 to Leu-180.
829368	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 672 as residues: Glu-1 to Tyr-7, Pro-13 to Glu-24, Arg-31 to Ile-39, Gln-59 to Lys-65, His-67 to Leu-74.
829751	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 673 as residues: Ala-29 to Arg-45, Ser-48 to Glu-59, Lys-73 to Trp-79, Ala-100 to Ser-109.
829934	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 675 as residues: Arg-1 to Arg-6, Ser-46 to Asp-71, Glu-76 to Glu-90, Gln-107 to Tyr-118, Ser-124 to Asp-131, Glu-163 to Asp-170, Ala-239 to Asp-245, Asp-262 to Arg-268, Gln-276 to Asp-283, Arg-293 to Lys-300, Ser-307 to Glu-313, Phe-346 to Phe-351, Phe-361 to Ala-373.
829951	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 677 as residues: Thr-21 to Lys-28.
830173	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 678 as residues: Gly-51 to Asn-68, Thr-75 to Lys-82, Ala-86 to Ala-97, Asn-99 to Arg-106, Leu-121 to Phe-126, Ala-155 to Ser-163, Asp-175 to Asp-180, Ala-184 to Phe-196, Leu-204 to Asn-214, Asp-219 to Gln-232, Leu-269 to Arg-274, Pro-392 to Pro-400, Thr-430 to Asn-437, Tyr-472 to Gln-477, Leu-483 to Gln-499, Asn-516 to Gln-524, Ser-533 to Gln-546, Lys-562 to Glu-576, Leu-589 to Ala-594, Asp-624 to Ala-633, Ile-741 to Asp-746, Val-817 to Lys-839, Tyr-872 to Lys-878, Thr-929 to Asp-940.
830365	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 680 as residues: Trp-36 to Glu-41, Asp-71 to Arg-76, Asn-80 to Gly-87, Arg-103 to Pro-115.
830456	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 681 as residues: Leu-48 to Cys-54.
830549	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 682 as residues: Ser-1 to Pro-24, Pro-40 to Thr-50, Glu-62 to Gly-83, Arg-103 to Leu-108, Ser-141 to Lys-146, Lys-184 to Ser-190.
830602	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 683 as residues: Arg-53 to Thr-63, Ile-100 to Lys-108.
830610	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 684 as residues: Pro-27 to Cys-32, Ala-61 to Gly-70, Pro-76 to Gly-85, Met-115 to Gly-120, Glu-162 to Lys-171, Pro-222 to Tyr-228, Glu-242 to Thr-248, Lys-261 to Gly-269.
830644	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 685 as residues: Ile-1 to Ser-10.
830707	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 686 as residues: Asn-34 to Leu-53, Gln-61 to Leu-67.

830709	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 687 as residues: Arg-13 to Gln-18, Pro-22 to Ala-40, Ala-66 to Asp-84, Glu-94 to Arg-101.
830733	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 688 as residues: Glu-1 to Asp-8.
830855	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 690 as residues: Ser-1 to His-6.
830949	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 691 as residues: Arg-5 to Arg-12, Gly-25 to Trp-30, Thr-77 to Trp-96, Thr-101 to Glu-106, Gly-109 to Arg-127.
830965	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 692 as residues: Leu-24 to Arg-56, Pro-83 to Arg-90, Ile-110 to Ile-115, Lys-123 to Val-136.
830973	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 693 as residues: Ser-1 to Asn-7, Tyr-13 to Asp-23.
830989	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 695 as residues: Cys-2 to Ser-16, Glu-55 to Lys-61, Pro-83 to Leu-88, Ser-135 to Pro-148, Val-152 to Arg-163, Pro-223 to Thr-230, Ala-242 to Val-253, Arg-258 to Glu-274, Gly-290 to Asp-300, Lys-337 to Asn-345, Asp-373 to Ala-398, Gly-401 to Lys-406, Gln-410 to Ala-430, Pro-433 to Gln-460.
831134	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 696 as residues: Ala-19 to His-24.
831200	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 697 as residues: Trp-1 to Gly-6.
831531	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 699 as residues: Ser-94 to Asn-116, Glu-139 to Asp-155, Tyr-190 to Leu-195, Ile-230 to Ile-235, Ser-309 to Glu-317.
831665	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 700 as residues: Leu-4 to Trp-12.
831724	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 701 as residues: Pro-26 to Lys-32.
831884	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 702 as residues: Pro-46 to Ala-52, Thr-68 to Trp-86, Arg-91 to Arg-96, Lys-127 to Asp-141.
831897	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 703 as residues: Pro-10 to Ser-20, Val-73 to Ser-78, Asp-123 to Glu-134, Leu-138 to Val-149, Ala-181 to Ala-187, Thr-189 to Val-196, Arg-213 to Gln-224.
831922	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 704 as residues: Leu-32 to Asp-37, Ile-43 to Asn-49.
832266	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 707 as residues: Ala-73 to Arg-79.
832309	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 708 as residues: Val-10 to Gly-15, Ser-98 to Thr-105.
832342	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 709 as residues: Pro-9 to Trp-16, Thr-66 to Ser-72.
832351	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 710 as residues: Asp-16 to Val-21, Leu-54 to Asp-71.
832352	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 711 as residues: Asp-16 to Val-21, Leu-33 to Asp-50.
832434	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 712 as residues: Tyr-15 to Glu-23, Ser-46 to Arg-51, Gln-56 to Trp-61, Pro-79 to Lys-86.
832490	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 713 as residues: Arg-16 to Gly-23, Ala-37 to Asp-46, Asp-91 to Asp-97.
832573	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 714 as residues: Ala-9 to Gln-16, Glu-21 to Arg-27, Gly-66 to Pro-72.
833394	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 716 as residues: Glu-1 to Gly-6, Asp-12 to Gly-22, Ile-28 to Gln-33, Cys-86 to Gly-92, Gly-96 to Ile-105.
835355	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 717 as

	residues: Glu-8 to Ser-15, Gly-42 to Leu-49, Pro-73 to Gly-79, Tyr-82 to Arg-87, Ser-109 to Gly-118, Glu-122 to Ile-128, Asp-132 to Gly-137, Asp-146 to Arg-151, Pro-153 to Lys-158, Gly-191 to His-197, Tyr-210 to Ser-218, Lys-234 to Gly-239, Ala-246 to Ala-252, His-257 to Pro-268, Ser-274 to Gly-280, Pro-316 to Tyr-323, Ile-358 to Leu-363, Gln-375 to Tyr-381, Gln-390 to Tyr-397, Gln-418 to Cys-430.
835497	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 718 as residues: Glu-141 to Pro-151, Asp-179 to Glu-184, Gly-214 to Ser-219, Thr-226 to Tyr-231, Thr-239 to Gly-248, Pro-281 to Gly-297, Pro-326 to Arg-336, Gln-408 to Asp-416.
835978	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 720 as residues: Trp-25 to Val-31.
836274	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 722 as residues: Ser-1 to Glu-9.
836731	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 723 as residues: Lys-15 to Glu-22, Gly-25 to Ala-34, Glu-75 to Gly-81, Gln-91 to Val-100, Pro-146 to Glu-155, Gln-161 to Phe-167, Asn-170 to Gly-178.
838014	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 724 as residues: Arg-1 to Pro-10, Asp-170 to Pro-176, Arg-203 to Tyr-212, Gly-228 to Lys-235.
838874	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 725 as residues: Gln-30 to Gln-45.
839120	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 726 as residues: Thr-22 to Arg-27, Arg-69 to Gly-75, Leu-77 to Pro-85.
839611	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 727 as residues: Asp-12 to Thr-17.
840138	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 728 as residues: Ser-1 to Thr-10.
840616	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 729 as residues: Lys-93 to Gly-99, Glu-144 to Leu-160, Ser-265 to Asp-270, Thr-382 to Gln-396, Val-512 to Val-517, Glu-519 to Asp-535.
840780	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 730 as residues: Leu-8 to Gly-14, Pro-151 to Glu-157.
840857	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 731 as residues: Gln-7 to Glu-22, Ala-27 to Arg-46, Ser-138 to Lys-147, Lys-158 to Pro-163, Asn-171 to Glu-187, Glu-202 to Val-208, Glu-234 to Gly-240, Ser-253 to Lys-260, Gln-272 to Pro-279, Arg-292 to Glu-307, Arg-310 to Arg-317, Asp-342 to Gly-351, Pro-367 to Gly-375, Pro-378 to Arg-388, Leu-425 to Ala-447, Arg-536 to Asp-544, Lys-551 to Lys-561, Val-599 to Asp-604, Ser-622 to Ala-630, Pro-653 to Phe-659, Thr-666 to Ile-673, Pro-699 to Phe-705, Asn-709 to Gly-719, Ala-725 to Phe-737.
840862	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 732 as residues: Arg-2 to Pro-12, Lys-32 to Asn-37, His-75 to Asn-82.
840864	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 733 as residues: Pro-17 to Arg-30, Cys-34 to Gly-40, Met-74 to Glu-81, Pro-106 to Asp-111, Val-136 to Cys-147, Asn-192 to Asp-198.
840938	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 735 as residues: Ser-140 to Thr-148, Thr-194 to Lys-202.
841884	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 736 as residues: Thr-34 to Glu-47.
842241	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 737 as residues: Thr-92 to Lys-101, Glu-134 to Thr-142, Glu-149 to Lys-155, Trp-179 to Ser-187, Thr-205 to Arg-211, Ser-218 to Tyr-225, Asp-283 to Gln-290, Glu-292 to Ile-302, Asn-304 to Met-315.
843712	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 738 as residues: Arg-10 to Asn-16, Ala-59 to Pro-67.
844040	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 739 as residues: Phe-59 to Glu-68, Lys-105 to Gly-111.
844617	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 742 as

	residues: Arg-1 to Lys-7.
846187	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 745 as residues: Gly-8 to Gly-14, Gly-41 to Glu-48, Glu-54 to Lys-74, Glu-87 to Arg-98, Thr-158 to Asn-166, Gly-247 to Ser-254, Gly-257 to Arg-277, Ala-437 to Ser-444, Lys-505 to Arg-510, Phe-519 to Tyr-525, Lys-531 to Pro-538, Gly-562 to Leu-571, Phe-606 to Val-613, Val-692 to Ala-697, Ser-705 to Leu-715, Leu-742 to Cys-747.
HANGA53R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 749 as residues: Arg-4 to Ser-9.
HAHCP93R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 752 as residues: Ser-1 to Ser-12, Thr-23 to Arg-28.
HBGAA76R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 753 as residues: Ser-4 to Ser-11, Pro-27 to Asn-37.
HTXPI29R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 756 as residues: Thr-17 to Leu-24, Thr-57 to Tyr-67, Leu-92 to Phe-102, Asn-128 to Gln-134.
HBGAA54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 760 as residues: Arg-62 to Leu-70, Ile-74 to Arg-79.
HDPJR77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 763 as residues: Glu-7 to Lys-22, Thr-33 to Glu-39, Lys-69 to Glu-76, Asp-84 to Tyr-90.
HTTIO41R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 764 as residues: Val-17 to Ser-22, Arg-41 to Glu-46, Lys-50 to Pro-75, Ser-92 to Pro-100.
HDPUL86R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 767 as residues: Lys-7 to Gly-13.
HTXNT16R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 768 as residues: Leu-67 to Asn-72, Thr-102 to Phe-111, Gly-127 to Gln-135.
HLXNA54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 770 as residues: Gln-1 to Glu-6, Pro-23 to Trp-31, Arg-46 to Trp-51.
H2LAX93R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 772 as residues: Glu-3 to Gln-10.
HWAFW10R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 773 as residues: Glu-13 to Asp-22, His-34 to Trp-40, Arg-69 to Lys-75.
HBGDD17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 775 as residues: Arg-23 to Thr-28, Pro-40 to Glu-51, Ala-62 to His-68.
H2CBB43R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 778 as residues: Asp-90 to Asp-95, Arg-106 to Thr-117.
H2CBQ77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 779 as residues: Asp-11 to Glu-16, Gln-19 to Tyr-24, Pro-34 to Gly-46.
HOEMK06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 781 as residues: Pro-1 to Gln-14.
HCHAG30R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 783 as residues: Gly-1 to Trp-7.
HAEA126R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 788 as residues: Lys-32 to Val-40, Arg-43 to Pro-51.
H2CBN76R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 791 as residues: Ala-17 to Leu-22, Thr-72 to Lys-77.
HAGFX49R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 792 as residues: Ala-10 to Leu-15, His-64 to Cys-71.
HTXKR32R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 794 as residues: Ser-2 to Gly-12, Glu-57 to Val-65.
H6EAF46R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 796 as residues: Arg-11 to Ser-21.
H2LAK40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 798 as residues: Glu-11 to Lys-20, Pro-22 to Arg-28.
H2LAY71R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 799 as residues: Arg-26 to Leu-36, Gln-82 to Asp-101, Arg-103 to Arg-108, Arg-113 to Arg-131.
HASAW80R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 803 as

	residues: Gly-1 to Arg-6, Ala-19 to Pro-27, Gly-34 to Phe-40.
HCHAF25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 804 as residues: Ser-30 to Thr-40, Leu-78 to Val-85, Asp-92 to Ala-97.
HLTHH84R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 805 as residues: Glu-2 to Ala-8.
HADDC09R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 808 as residues: Leu-3 to Gly-9, Thr-20 to Gly-29.
HAQA110R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 811 as residues: Gly-1 to Lys-21.
HBGBT78R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 814 as residues: Asn-1 to Lys-22.
HBGCB06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 815 as residues: Phe-1 to Phe-15.
HCHMW05R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 823 as residues: Pro-6 to Ser-11.
HODFW25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 829 as residues: Ser-1 to Thr-8, Glu-17 to Ala-32, Arg-39 to Trp-47.
HOEMQ91R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 830 as residues: Arg-8 to Ser-13.
HOGBG56R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 831 as residues: Lys-20 to Arg-25.



The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide sequence shown in SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or encoded by a polynucleotide that hybridizes to the complement of an epitope encoding sequence of SEQ ID NO:X, or an epitope encoding sequence contained in the deposited cDNA clone under stringent hybridization conditions, or alternatively, under lower stringency hybridization conditions, as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions, as defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at

least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985)). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice

are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention, and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995).

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for

immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).)

5        Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for  
10        convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., *Cell* 37:767 (1984).)

15        Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

20        Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., *Proc. Natl. Acad. Sci. USA* 88:8972- 897 (1991)). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto  
25        Ni<sup>2+</sup> nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

30        Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al.,

Curr. Opin. Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

As discussed herein, any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

In certain preferred embodiments, proteins of the invention comprise fusion proteins wherein the polypeptides are N and/or C- terminal deletion mutants. In preferred embodiments, the application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences encoding polypeptides having the amino acid sequence of the specific N- and C-terminal deletions mutants. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

#### 10 **Vectors, Host Cells, and Protein Production**

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include,

but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells.

5 Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-10 3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, 15 pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in 20 many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid 25 extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified 30 from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast,

higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to



the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYDI, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, 5 pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning 10 the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or 15 replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous 20 polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their 25 entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized 30 by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the

polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid,  $\gamma$ -Abu,  $\epsilon$ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, fluoro-amino acids, designer amino acids such as  $\beta$ -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

Non-naturally occurring variants may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (*see, e.g., Carter et al., Nucl. Acids Res. 13:4331 (1986); and Zoller et al., Nucl. Acids Res. 10:6487 (1982)*), cassette mutagenesis (*see, e.g., Wells et al., Gene 34:315 (1985)*), restriction selection mutagenesis (*see, e.g., Wells et al., Philos. Trans. R. Soc. London SerA 317:415 (1986)*).

The invention additionally, encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased

solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200; 500; 1000; 1500; 2000; 2500; 3000; 3500; 4000; 4500; 5000; 5500; 6000; 6500; 7000; 7500; 8000; 8500; 9000; 9500; 10,000; 10,500; 11,000; 11,500; 12,000; 12,500; 13,000; 13,500; 14,000; 14,500; 15,000; 15,500; 16,000; 16,500; 17,000; 17,500; 18,000; 18,500; 19,000; 19,500; 20,000; 25,000; 30,000; 35,000; 40,000; 50,000; 55,000; 60,000; 65,000; 70,000; 75,000; 80,000; 85,000; 90,000; 95,000; or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconj. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a

reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-

304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of  
5 proteins without an intervening linker employs tresylated MPEG, which is produced by the  
modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride  
( $\text{ClSO}_2\text{CH}_2\text{CF}_3$ ). Upon reaction of protein with tresylated MPEG, polyethylene glycol is  
directly attached to amine groups of the protein. Thus, the invention includes protein-  
polyethylene glycol conjugates produced by reacting proteins of the invention with a  
10 polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different  
intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is  
incorporated herein by reference, discloses urethane linkers for connecting polyethylene  
glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is  
15 attached to the protein by a linker can also be produced by reaction of proteins with  
compounds such as MPEG-succinimidylsuccinate, MPEG activated with  
1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-  
nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional  
polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to  
20 proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein  
by reference. Pegylated protein products produced using the reaction chemistries set out  
herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention  
(*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the  
25 invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more  
polyethylene glycol molecules. Similarly, the average degree of substitution within ranges  
such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17,  
16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for  
determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit.*  
30 *Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

The breast/ovarian cancer antigen polypeptides of the invention may be in monomers  
or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present

invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers,  
5 or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or an amino acid sequence encoded by SEQ ID NO:X, and/or an amino acid sequence encoded by the cDNA in a related cDNA clone  
10 contained in a deposited library (including fragments, variants, splice variants, and fusion proteins, corresponding to any one of these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the  
15 invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at  
20 least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric  
25 multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example,  
30 homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention

contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in a polypeptide encoded by SEQ ID NO:X, and/or by the cDNA in the related cDNA clone contained in a deposited library). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the

invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide



components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

### Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG,

IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain  
5 Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable  
10 region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human  
15 immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes  
20 of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553  
25 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described  
30 herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that

specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol.*

Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, but not limited to, to  
5 purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference  
10 herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other  
15 compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e., by the  
20 covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other  
25 protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method  
30 known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to

induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by

fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any

desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol. Methods* 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., *Nature* 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein*



Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent

No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed  
5 against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903  
10 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies  
15 which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For  
20 example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

#### *Polynucleotides Encoding Antibodies*

The invention further provides polynucleotides comprising a nucleotide sequence  
25 encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

30 The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be

assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework

regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038-1041 (1988)).

#### *Methods of Producing Antibodies*

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein.

Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not

limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or

factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells.

5 The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence  
10 of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan &  
15 Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can  
20 be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion  
25 desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end,  
30 eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, HeLa, COS,

MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp<sup>r</sup>t- or ap<sup>r</sup>t- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215; and hyg<sup>r</sup>, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.),



Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by  
5 reference herein in their entirety.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing  
10 antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the  
15 first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to  
20 avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method  
25 known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide  
30 sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or

portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20,  
5 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro  
10 immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of  
15 the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The  
20 polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the  
25 art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341(1992) (said references incorporated by reference in their entireties).

30 As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using

methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., *Nature* 331:84-86 (1988)). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995)).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent

materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99}\text{Tc}$ .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical

chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- $\alpha$ , TNF- $\beta$ , AIM I (See, 5 International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGF (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, 10 lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not 15 limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 20 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of 25 Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an 30 antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

### 5 *Immunophenotyping*

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types.

10 Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S.  
15 Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic  
20 stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

### *Assays For Antibody Binding*

The antibodies of the invention may be assayed for immunospecific binding by any  
25 method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays,  
30 immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel *et al.*, eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York,

which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

## ***Therapeutic Uses***

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of



the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities

include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

5

### *Gene Therapy*

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989).

In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the

host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdrl* gene to

5 hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

10 Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing

15 cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell*

20 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

25 Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to

30 a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method

known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes  
5 into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is  
10 expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

15 Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic  
20 stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible  
25 by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio.  
30 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that

expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

#### 15 *Therapeutic/Prophylactic Administration and Composition*

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral

routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al.,

J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

5 Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector  
10 and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868  
15 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means  
20 approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic  
25 origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate,  
30 glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form



of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend

on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

5 For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the  
10 foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more  
15 containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

20

### ***Diagnosis and Imaging***

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity  
25 of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide  
30 gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the

amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99m}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as positron emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule

is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

### *Kits*

5           The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present  
10   invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes  
15   the first antibody may be conjugated to a detectable substrate).

          In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated  
20   polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically  
25   synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

          In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of  
30   the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

#### **Uses of the Polynucleotides**

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The breast/ovarian cancer antigen polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can  
5 hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X, or the  
10 complement thereto. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

15 Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted  
20 chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This  
25 technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple  
30 sites and/or multiple chromosomes).

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 3 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

The polynucleotides of the present invention would likewise be useful for radiation  
5 hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000);  
10 and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular  
15 disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

20 Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all  
25 affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

30 Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the



invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention provides a method of detecting increased or decreased expression levels of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides in affected  
5 individuals as compared to unaffected individuals using polynucleotides of the present invention and techniques known in the art, including but not limited to the method described in Example 11. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis of a  
10 disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer, involving measuring the expression level of breast/ovarian cancer antigen polynucleotides in breast and/or ovarian tissue or other cells or body fluid from an individual and comparing the measured gene  
15 expression level with a standard breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer.

In still another embodiment, the invention includes a kit for analyzing samples for the  
20 presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe  
25 has one strand containing a 31' mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is  
30 useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression will experience a

worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of breast, ovarian, breast cancer and/or ovarian cancer polynucleotides" is intended qualitatively or quantitatively measuring or estimating  
5 the level of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the level of the mRNA encoding the breast, ovarian, breast cancer and/or ovarian cancer polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in a second biological sample).  
10 Preferably, the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the female reproductive system related disorder or being determined by averaging  
15 levels from a population of individuals not having a female reproductive system related disorder. As will be appreciated in the art, once a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an  
20 individual, body fluid, cell line, tissue culture, or other source which contains breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the corresponding mRNA. As indicated, biological samples include body fluids (such as vaginal pool, breast milk, lymph, sera, plasma, urine, semen, synovial fluid and spinal fluid) which contain the breast, ovarian, breast cancer and/or ovarian cancer polypeptide, breast and/or ovarian tissue, and other tissue  
25 sources found to express the breast, ovarian, breast cancer and/or ovarian cancer polypeptide. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a  
30 solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with breast, ovarian, breast cancer and/or ovarian cancer polynucleotides attached may

be used to identify polymorphisms between the breast, ovarian, breast cancer and/or ovarian cancer polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, though most preferably in breast and/or ovarian related proliferative, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses breast, ovarian, breast cancer and/or ovarian cancer polynucleotides that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, *Science* 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, *Nature* 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T<sub>sub.m</sub>) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in *Neoplastic Diseases of the Blood*, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., *supra*)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., *Proc. Natl. Acad. Sci.* 85:1028 (1988); Anfossi et al., *Proc. Natl. Acad. Sci.* 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not limited to treatment of proliferative disorders of hematopoietic

cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a breast/ovarian cancer antigen polynucleotide can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. *Neurochem.* 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., *Nucleic Acids Research* 6: 3073 (1979); Cooney et al., *Science* 241: 456 (1988); and Dervan et al., *Science* 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., *Nucl. Acids Res.* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. *Neurochem.* 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed

on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

5       The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA  
10 sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues,  
15 e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific  
20 polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular  
25 tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to breast, ovarian, breast cancer and/or ovarian cancer polynucleotides prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue  
30 cultures for contamination.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample.

Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower  
5 levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, breast, ovarian, breast cancer and/or ovarian cancer tissues and/or cancerous and/or wounded tissues) or bodily fluids (e.g., vaginal pool, breast milk, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder,  
10 relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in  
15 the assayed gene expression level compared to the standard expression level is indicative of a disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the  
20 process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

#### Uses of the Polypeptides

25 Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J.  
30 Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for  
5 detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium  
10 ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ), molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ),  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying levels of polypeptide of the present invention in a biological  
15 sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be  
20 incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ , ( $^{131}\text{I}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{115\text{m}}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{112}\text{In}$ ,  $^{111}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ,  $^{99\text{m}}\text{Tc}$ ), thallium ( $^{201}\text{Tl}$ ), gallium ( $^{68}\text{Ga}$ ,  $^{67}\text{Ga}$ ), palladium ( $^{103}\text{Pd}$ ),  
25 molybdenum ( $^{99}\text{Mo}$ ), xenon ( $^{133}\text{Xe}$ ), fluorine ( $^{18}\text{F}$ ,  $^{153}\text{Sm}$ ,  $^{177}\text{Lu}$ ,  $^{159}\text{Gd}$ ,  $^{149}\text{Pm}$ ,  $^{140}\text{La}$ ,  $^{175}\text{Yb}$ ,  $^{166}\text{Ho}$ ,  $^{90}\text{Y}$ ,  $^{47}\text{Sc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{142}\text{Pr}$ ,  $^{105}\text{Rh}$ ,  $^{97}\text{Ru}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system  
30 used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or



antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ , or other radioisotopes such as, for example,  $^{103}\text{Pd}$ ,  $^{133}\text{Xe}$ ,  $^{131}\text{I}$ ,  $^{68}\text{Ge}$ ,  $^{57}\text{Co}$ ,  $^{65}\text{Zn}$ ,  $^{85}\text{Sr}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{90}\text{Y}$ ,  $^{153}\text{Sm}$ ,  $^{153}\text{Gd}$ ,  $^{169}\text{Yb}$ ,  $^{51}\text{Cr}$ ,  $^{54}\text{Mn}$ ,  $^{75}\text{Se}$ ,  $^{113}\text{Sn}$ ,  $^{90}\text{Yttrium}$ ,  $^{117}\text{Tin}$ ,  $^{186}\text{Rhenium}$ ,  $^{166}\text{Holmium}$ , and  $^{188}\text{Rhenium}$ ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; 5 and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer polypeptide of the present invention in cells or body fluid of an individual, or more  
10 preferably, assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer of the present invention in breast and/or ovarian cells or vaginal pool or breast milk of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With  
15 respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or  
20 further progression of the cancer.

Moreover, breast/ovarian cancer antigen polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or  
25 cancerous diseases and conditions, preferably proliferative disorders of the breast and/or ovary, and/or cancerous disease and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the  
30 activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing

inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example, administration  
5 of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular  
10 weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

15

#### Gene Therapy Methods

Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an  
20 animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

25

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Beldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer  
30 Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996);

Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-

actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into  
5 cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis,  
10 ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the  
15 lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example,  
20 stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more  
25 preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

30 The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues,

throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical  
5 administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

10 In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have  
15 been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

20 Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include  
25 transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes  
30 is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG),  
5 dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can  
10 be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat  
15 Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

20 The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by  
25 depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate  
30 solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to

the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* (1979) 17:77); ether injection (Deamer, D. and Bangham, A., *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977) 76:836; Fraley et al.,  
5 *Proc. Natl. Acad. Sci. USA* (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., *Proc. Natl. Acad. Sci. USA* (1979) 76:145); and reverse-phase evaporation (REV) (Fraley et al., *J. Biol. Chem.* (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., *Proc. Natl. Acad. Sci. USA* (1978) 75:145; Schaefer-Ridder et al., *Science* (1982) 215:166), which are  
10 herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the  
15 injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S.  
20 Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include,  
25 but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are  
30 not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, *Human Gene Therapy* 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector



may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and  $\text{CaPO}_4$  precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

5       The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polypeptide of the present invention.

10       In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have  
15       been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) Am. Rev. Respir. Dis. 109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive  
20       studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

      Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al.,  
25       Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to  
30       Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc.

Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

Preferably, the polynucleotide encoding a polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the

cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppository solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such

carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

#### 15 **Biological Activities**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

#### **Immune Activity**

A polypeptide or polynucleotide, or agonists or antagonists of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides or polypeptides, or

agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells.

5 Polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g.  
10 agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

15 Moreover, polynucleotides or polypeptides, or agonists or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia,  
20 factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides or polypeptides, or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

25 Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides or polypeptides, or agonists or  
30 antagonists of the present invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, 5 Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic 10 asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention 15 may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that 20 inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation 25 and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, 30 Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

**Hyperproliferative Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may  
5 inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing  
10 T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by  
15 Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

20 Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease,  
25 histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

30 Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.



Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403

(1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral  
5 (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-  
10 dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time  
15 of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

20 Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells.

25 The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

30 The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal

antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-6}M$ ,  $10^{-6}M$ ,  $5 \times 10^{-7}M$ ,  $10^{-7}M$ ,  $5 \times 10^{-8}M$ ,  $10^{-8}M$ ,  $5 \times 10^{-9}M$ ,  $10^{-9}M$ ,  $5 \times 10^{-10}M$ ,  $10^{-10}M$ ,  $5 \times 10^{-11}M$ ,  $10^{-11}M$ ,  $5 \times 10^{-12}M$ ,  $10^{-12}M$ ,  $5 \times 10^{-13}M$ ,  $10^{-13}M$ ,  $5 \times 10^{-14}M$ ,  $10^{-14}M$ ,  $5 \times 10^{-15}M$ , and  $10^{-15}M$ .

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998),

which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

5 Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1  
10 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the  
15 expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

20 Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top  
25 Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

30 In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with

heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

#### 10 **Cardiovascular Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, heart murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomas, bacillary angiomas, Hippiel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, ataxia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a

Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

#### Anti-Angiogenesis Activity

5       The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and  
10   spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye  
15   disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological  
20   conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

      The polynucleotides encoding a polypeptide of the present invention may be administered along with other polynucleotides encoding an angiogenic protein. Examples of  
25   angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide  
30   synthase.

      The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the



invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including breast, ovarian, prostate, lung, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid

arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque  
5 neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar  
10 or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of  
15 hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental  
20 fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular  
25 degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating  
30 neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation

of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbal corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbal cornea interspersed between the corneal lesion and its undesired

potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

- 5        Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma.
- 10       Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a
- 15       therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

- Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist
- 20       in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

- Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such
- 25       that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

- Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic
- 30       joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated with the the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochela minalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated

with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site. (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for  
5 example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate,  
10 sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide,  
15 molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine  
20 sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline,  
25 alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium  
30 Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-

chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolimidazole; and metalloproteinase inhibitors such as BB94.

5 **Diseases at the Cellular Level**

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon  
10 cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary  
15 cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression,  
20 and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute  
25 lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not  
30 limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's



tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

#### **Wound Healing and Epithelial Cell Proliferation**

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity

wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and  
5 antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to  
10 stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness  
15 graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

20 It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes,  
25 type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

30 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on

the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or

polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

## Neurological Diseases

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as

cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, 5 Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis, cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease, cerebral amyloid angiopathy, cerebral 10 aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar 15 insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache, migraine, dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis 20 periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy 25 which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, Hallervorden-Spatz Syndrome, hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as 30 hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous

system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, cerebral malaria, meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis. Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uve-meningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie) cerebral toxoplasmosis, central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sclerolysis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolysaccharidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as

holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta, hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary  
5 optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing  
10 loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering,  
15 voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus,  
20 Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color  
25 vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as  
30 spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex

Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, Diabetic neuropathies such as diabetic foot, nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

### Infectious Disease

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.



Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia

(e.g., *Borrelia burgdorferi*, Brucellosis, Candidiasis, *Campylobacter*, *Coccidioidomycosis*, Cryptococcosis, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacteriaceae (*Klebsiella*, *Salmonella* (e.g., *Salmonella typhi*, and *Salmonella paratyphi*), *Serratia*, *Yersinia*), *Erysipelothrix*, *Helicobacter*,  
5 Legionellosis, Leptospirosis, *Listeria*, Mycoplasmatales, *Mycobacterium leprae*, *Vibrio cholerae*, Neisseriaceae (e.g., *Acinetobacter*, Gonorrhea, Meningococcal), *Meisseria meningitidis*, Pasteurellacea Infections (e.g., *Actinobacillus*, *Heamophilus* (e.g., *Heamophilus influenza type B*), *Pasteurella*), *Pseudomonas*, Rickettsiaceae, Chlamydiaceae, Syphilis, *Shigella* spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g.,  
10 *Streptococcus pneumoniae* and Group B *Streptococcus*). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme  
15 Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections.  
20 Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Ppolynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diphtheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated or  
25 detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and *Trichomonas* and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparum*,  
30 *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic

infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

#### Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects.

A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

#### **Chemotaxis**

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

#### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules  
5 include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide  
10 binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the  
15 expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled  
20 competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound  
25 with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the  
30 polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand

panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a  
5 cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

10 Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be  
15 photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide  
20 probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S.  
25 Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and  
30 corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding

polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and  $^3\text{[H]}$  thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of  $^3\text{[H]}$  thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of  $^3\text{[H]}$  thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the

present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

### **Targeted Delivery**

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method



for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

5 In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector  
10 systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an  
15 inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be  
20 used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

## 25 **Drug Screening**

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of  
30 having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the

polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells  
5 which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other  
10 agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is  
15 separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and  
20 is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known  
25 in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention  
30 specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

**Antisense And Ribozyme (Antagonists)**

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the cDNA contained in the related cDNA clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the

production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., *Nature* 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most

efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre et al., 1987, *Proc. Natl. Acad. Sci.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, *BioTechniques* 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine,

2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 5 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, 10 and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or 15 analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-0- 20 methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides 25 may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

30 Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at

site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'.

5 The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the  
10 intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding  
15 DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

20 Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and  
25 prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

30 The antagonist/agonist may also be employed to treat the diseases described herein.

Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with

overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

## 5 Other Activities

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The  
10 polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells  
15 and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's  
20 disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be  
25 also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and  
30 differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.



A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

#### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least  
5 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the  
10 deposit.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

15 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a  
20 sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and  
25 determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected  
30 from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a

nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X; or the cDNA in the related cDNA clone identified in Table 1 which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for diagnosing a pathological condition which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the

group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

5 Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous  
10 nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the cDNA clone referenced in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least  
15 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least  
20 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a  
25 polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

30 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by the cDNA clone referenced in Table 1; a polypeptide encoded by SEQ ID NO:X; and/or the polypeptide sequence of SEQ ID NO:Y.

5 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid  
10 sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide  
15 comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is a method for detecting in a biological sample a polypeptide  
20 comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule  
25 in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from  
30 said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in

a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of:

polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.



Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

*Examples**Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample*

5 Each deposited cDNA clone is contained in a plasmid vector. Table 5 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a  
 10 particular clone is identified in Table 5 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
15	Zap Express	pBK
	lalfmid BA	plafmid BA
	pSportI	pSportI
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
20	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altling-Mees, M. A. and Short, J. M., Nucleic Acids Res. 25 17:9494 (1989)) and pBK (Altling-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3  
 30

primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

5 Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 5, as well as the corresponding plasmid vector sequences designated above.

15 The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 2 and 5 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone referenced in Table 1.

TABLE 5

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lambda ZAP II	LP01
HMEA HMEC HMED HMEE HMEF HMEG HMEI HMEJ HMEK HMEL	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM	Human Striatum Depression, re-rescue	Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, fract. A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02
HCUA HCUB HCUC	CD34 depleted Buffy Coat (Cord Blood)	ZAP Express	LP02
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUJ	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
HHTM HHTN HHTO	H. hypothalamus, fract. A; re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, fract. A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI	Human Gall Bladder	Uni-ZAP XR	LP03
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ	Human Fetal Lung III	Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPF	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
HAPA HAPB HAPC HAPM	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE HETF HETG HETH HETI	Human Endometrial Tumor	Uni-ZAP XR	LP03
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
HHPB HHPD HHPF HHPG HHPH	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUV C HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD HTAE	Human Activated T-Cells	Uni-ZAP XR	LP03
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
HJPA HJPB HJPC HJPD	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTF	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
HCAA HCAB HCAC	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
HFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
HBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HHPS	Human Hippocampus, subtracted	pBS	LP03
HKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
HRGS	Raji cells, cyclohexamide treated, subtracted	pBS	LP03
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
HT4S	Activated T-Cells, 12 hrs, subtracted	Uni-ZAP XR	LP03
HCD A HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
HTLA HTLB HTLC HTLD HTLE	Human adult testis, large inserts	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTLF			
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine labelledEco	Uni-ZAP XR	LP03
HNFA HNFB HNFC HNFD HNFE HNFF HNFG HNFH HNFJ	Human Neutrophil, Activated	Uni-ZAP XR	LP03
HTOB HTOC	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS (treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
HBCA HBCB	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re-excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re- excision	pBS	LP03
HMBB HBMC HBMD	Human Bone Marrow, re-excision	pBS	LP03
HKML HKMM HKMN	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	HL-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03
HTXJ HTXK	Activated T-cell(12h)/Thiouridine-re- excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSD HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03
HAGA HAGB HAGC HAGD HAGE HAGF	Human Amygdala	Uni-ZAP XR	LP03
HSRA HSRB HSRE	STROMAL -OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE	Stromal cell TF274	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HSQF HSQG			
HSKA HSKB HSKC HSKD HSKE HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLE HSLF HSLG	Smooth muscle, control	Uni-ZAP XR	LP03
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex, epileptic, re-excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced, re-exc	pBS	LP03
HFCA HFCB HFCC HFCD HFCE HFCF	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK	Human Synovial Sarcoma	Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
HEPA HEPB HEPD	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNC HSND HSNE HSNF HSNH HSNJ HSNK HSNL HSNM HSNN	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTB HWTG HWTJ	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04
HISB	Salivary gland, re-excision	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP04
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH	Endothelial-induced	Uni-ZAP XR	LP04
HBIA HBIB HBIC	Human Brain, Striatum	Uni-ZAP XR	LP04
HISA HISB HISD HISE	Human Hypothalamus, Schizophrenia	Uni-ZAP XR	LP04
HNGA HNCB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ	neutrophils control	Uni-ZAP XR	LP04
HNHA HNHB HNHC HNHD HNHE HNHG HNHG HNHG HNHG HNHG HNHG	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04
HSDB HSDC	STRIATUM DEPRESSION	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HHPT	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNF $\alpha$ and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAG HMAE HMAF HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
HPHA	Normal Prostate	Uni-ZAP XR	LP04
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP04
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
HMAJ HMAK	H Macrophage (GM-CSF treated), re-excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimers, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04
HMIA HMIB HMIC	Human Manic Depression Tissue	Uni-ZAP XR	LP04
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
HJBA HJBB HJBC HJBD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF- $\alpha$	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
HONA	Normal Ovary, Premenopausal	pBS	LP05
HARA HARB	Human Adult Retina	pBS	LP05
HLJA HLJB	Human Lung	pCMVSPORT 1	LP06
HOFM HOFN HOFO	H. Ovarian Tumor, II, OV5232	pCMVSPORT 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSPORT 2.0	LP07
HCGL	CD34+cells, II	pCMVSPORT 2.0	LP07
HDLA	Hodgkin's Lymphoma I	pCMVSPORT 2.0	LP07
HDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSPORT 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSPORT2.0	LP07
HCIM	CAPFINDER, Crohn's Disease, lib 2	pCMVSPORT 2.0	LP07
HKAL	Keratinocyte, lib 2	pCMVSPORT2.0	LP07
HKAT	Keratinocyte, lib 3	pCMVSPORT2.0	LP07
HNDA	Nasal polyps	pCMVSPORT2.0	LP07
HDRA	H. Primary Dendritic Cells, lib 3	pCMVSPORT2.0	LP07



Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOHA HOHB HOHC	Human Osteoblasts II	pCMVSPORT2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSPORT3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSPORT3.0	LP08
HMTA	pBMC stimulated w/ poly I/C	pCMVSPORT3.0	LP08
HNTA	NTERA2. control	pCMVSPORT3.0	LP08
HDP A HDPB HDP C HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSPORT3.0	LP08
HDP M HDPN HDPO HDPP	Primary Dendritic cells, frac 2	pCMVSPORT3.0	LP08
HMUA HMUB HMUC	Myeloid Progenitor Cell Line	pCMVSPORT3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSPORT3.0	LP08
HHEM HHEN HHEO HHEP	T cell helper II	pCMVSPORT3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSPORT3.0	LP08
HJMA HJMB	Human endometrial stromal cells-treated with progesterone	pCMVSPORT3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells-treated with estradiol	pCMVSPORT3.0	LP08
HSYA HSYB HSYC	Human Thymus Stromal Cells	pCMVSPORT3.0	LP08
HLWA HLWB HLWC	Human Placenta	pCMVSPORT3.0	LP08
HRAA HRAB HRAC	Rejected Kidney, lib 4	pCMVSPORT3.0	LP08
HMTM	PCR, pBMC I/C treated	PCR II	LP09
HMJA	H. Meningioma, M6	pSport 1	LP10
HMKA HMKB HMKC HMKD HMKE	H. Meningioma, M1	pSport 1	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport 1	LP10
HOFA	Ovarian Tumor I, OV5232	pSport 1	LP10
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport 1	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport 1	LP10
HADA HADC HADD HADE HADF HADG	Human Adipose	pSport 1	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10
HTWB HTWC HTWD HTWE HTWF	Resting T-Cell Library, II	pSport 1	LP10
HMMA	Spleen metastatic melanoma	pSport 1	LP10
HLYA HLYB HLYC HLYD HLYE	Spleen, Chronic lymphocytic leukemia	pSport 1	LP10
HCGA	CD34+ cell, I	pSport 1	LP10
HEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport 1	LP10
HSPA	Salivary Gland, Lib 2	pSport 1	LP10
HCHA HCHB HCHC	Breast Cancer cell line, MDA 36	pSport 1	LP10
HCHM HCHN	Breast Cancer Cell line, angiogenic	pSport 1	LP10
HCIA	Crohn's Disease	pSport 1	LP10
HDAA HDAB HDAC	HEL cell line	pSport 1	LP10
HABA	Human Astrocyte	pSport 1	LP10
HUFA HUFB HUFC	Ulcerative Colitis	pSport 1	LP10
HNTM	NTERA2 + retinoic acid, 14 days	pSport 1	LP10
HDQA	Primary Dendritic cells, CapFinder2, frac 1	pSport 1	LP10
HDQM	Primary Dendritic Cells, CapFinder, frac 1	pSport 1	LP10

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	2		
HLDX	Human Liver, normal.CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells,untreated	pSport1	LP10
HUMA	Human Dermal Endothelial cells.treated	pSport1	LP10
HCJA	Human Stromal Endometrial fibroblasts, untreated	pSport1	LP10
HCJM	Human Stromal endometrial fibroblasts, treated w/ estradiol	pSport1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport1	LP10
HFNA	Human ovary tumor cell OV350721	pSport1	LP10
HKGA HKGB HKGC HKGD	Merkel Cells	pSport1	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport1	LP10
HLSA	Skin, burned	pSport1	LP10
HBZA	Prostate.BPH, Lib 2	pSport 1	LP10
HBZS	Prostate BPH,Lib 2, subtracted	pSport 1	LP10
HFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
HFII HFIL HFIJ	Synovial hypoxia	pSport 1	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport 1	LP10
HGCA	Mesangial cell, frac 1	pSport1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport1	LP10
HFIX HFYI HFIZ	Synovial Fibroblasts (III/TNF), subt	pSport1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSPORT 1	LP012
HHBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSPORT 1	LP012
HBBA HBBB	Human Brain	pCMVSPORT 1	LP012
HLJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSPORT 1	LP012
HOGA HOGB HOGC	Ovarian Tumor	pCMVSPORT 2.0	LP012
HTJM	Human Tonsils, Lib 2	pCMVSPORT 2.0	LP012
HAMF HAMG	KMH2	pCMVSPORT 3.0	LP012
HAJA HAJB HAJC	L428	pCMVSPORT 3.0	LP012
HWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSPORT 3.0	LP012
HWAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSPORT 3.0	LP012
HYAA HYAB HYAC	B Cell lymphoma	pCMVSPORT 3.0	LP012
HWHG HWHH HWHI	Healing groin wound, 6.5 hours post incision	pCMVSPORT 3.0	LP012
HWHP HWHQ HWHR	Healing groin wound; 7.5 hours post incision	pCMVSPORT 3.0	LP012
HARM	Healing groin wound - zero hr post-incision (control)	pCMVSPORT 3.0	LP012
HBIM	Olfactory epithelium; nasalcavity	pCMVSPORT 3.0	LP012
HWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSPORT 3.0	LP012
HWEA	Healing Abdomen Wound;15 days post incision	pCMVSPORT 3.0	LP012
HWJA	Healing Abdomen Wound:21&29 days	pCMVSPORT 3.0	LP012
HNAL	Human Tongue, frac 2	pSport1	LP012
HMJA	H. Meningima, M6	pSport1	LP012
HMKA HMKB HMKC HMKE	H. Meningima, M1	pSport1	LP012

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOFA	Ovarian Tumor I, OV5232	pSport I	LP012
HCFA HCFB HCFC HCFC	T-Cell PHA 16 hrs	pSport I	LP012
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport I	LP012
HMMA HMMB HMMC	Spleen metastatic melanoma	pSport I	LP012
HTDA	Human Tonsil, Lib 3	pSport I	LP012
HDBA	Human Fetal Thymus	pSport I	LP012
HDDA	Pericardium	pSport I	LP012
HBZA	Prostate, BPH, Lib 2	pSport I	LP012
HWCA	Larynx tumor	pSport I	LP012
HWKA	Normal lung	pSport I	LP012
HSMB	Bone marrow stroma, treated	pSport I	LP012
HBHM	Normal trachea	pSport I	LP012
HLFC	Human Larynx	pSport I	LP012
HLRB	Siebben Polyposis	pSport I	LP012
HNIA	Mammary Gland	pSport I	LP012
HNJB	Palate carcinoma	pSport I	LP012
HNKA	Palate normal	pSport I	LP012
HMZA	Pharynx carcinoma	pSport I	LP012
HABG	Cheek Carcinoma	pSport I	LP012
HMZM	Pharynx Carcinoma	pSport I	LP012
HDRM	Larynx Carcinoma	pSport I	LP012
HVAA	Pancreas normal PCA4 No	pSport I	LP012
HICA	Tongue carcinoma	pSport I	LP012
HUKA HUKB HUKC HUKD HUKF	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP013
HMEB	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor, re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HLIS	LNCAP, differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression, subtracted	pBluescript	LP013
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
HSBA HSBB HSBC HSBM	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
HJBA HJBB HJBC HJBD	Jurkat T-cell, S1 phase	pBluescript SK-	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
HAHA HAHB	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFC A HFCB HFCC HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTED HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTTE	Human Testes Tumor	Uni-ZAP XR	LP013
HYBA HYBB	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
HHFB HHFC HHFD HHFE HHFF	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUV C HUVD HUVE	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
HJPA HJPB HJPC HJPD	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
HCAA HCAB HCAC	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP013
HE9A HE9B HE9C HE9D HE9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage Human	Uni-ZAP XR	LP013
HE2B HE2C HE2F HE2G HE2P	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNE D HNEE	Human Neutrophil	Uni-ZAP XR	LP013
HGBA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
HROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
HBJA HBJB HBJC HBJD HBJE	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
HCPA	Corpus Callosum	Uni-ZAP XR	LP013
HSOA	stomach cancer (human)	Uni-ZAP XR	LP013
HERA	SKIN	Uni-ZAP XR	LP013
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HWTA HWTB HWTC	Wilms' tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPO HAPR HAQO HAPR	Human Adult Pulmonary; re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma; re-excision	Uni-ZAP XR	LP013
HAHC HAHD HAHE	Human Adult Heart; re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-IL1b induced	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP013
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma, TNF&LPS ind	Uni-ZAP XR	LP013
HMCF HMCB HMCH HMCI HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala; re-excision	Uni-ZAP XR	LP013
HACA	H. Adipose Tissue	Uni-ZAP XR	LP013
HKFB	K562 + PMA (36 hrs); re-excision	ZAP Express	LP013
HCWT HCWU HCWV	CD34 positive cells (cord blood); re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP013
HAVM	Temporal cortex-Alzheimer	pT-Adv	LP014
HAVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HHAS	CHME Cell Line	Uni-ZAP XR	LP014
HAJR	Larynx normal	pSport I	LP014
HWLE HWLF HWLG HWLH	Colon Normal	pSport I	LP014
HCRM HCRN HCRO	Colon Carcinoma	pSport I	LP014
HWLI HWLJ HWLK	Colon Normal	pSport I	LP014
HWLQ HWLR HWLS HWLT	Colon Tumor	pSport I	LP014
HBFM	Gastrocnemius Muscle	pSport I	LP014
HBOD HBOE	Quadriceps Muscle	pSport I	LP014
HBKD HBKE	Soleus Muscle	pSport I	LP014
HCCM	Pancreatic Langerhans	pSport I	LP014
HWGA	Larynx carcinoma	pSport I	LP014
HWGM HWGN	Larynx carcinoma	pSport I	LP014
HWLA HWLB HWLC	Normal colon	pSport I	LP014
HWLM HWLN	Colon Tumor	pSport I	LP014
HVAM HVAN HVAO	Pancreas Tumor	pSport I	LP014
HWGQ	Larynx carcinoma	pSport I	LP014
HAQM HAQN	Salivary Gland	pSport I	LP014
HASM	Stomach; normal	pSport I	LP014
HBCM	Uterus; normal	pSport I	LP014
HCDM	Testis; normal	pSport I	LP014
HDJM	Brain; normal	pSport I	LP014
HEFM	Adrenal Gland, normal	pSport I	LP014
HBAA	Rectum normal	pSport I	LP014
HFDH	Rectum tumour	pSport I	LP014
HGAM	Colon, normal	pSport I	LP014
HHMM	Colon, tumour	pSport I	LP014
HCLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
HRLA	L1 Cell line	ZAP Express	LP015

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HHAM	Hypothalamus, Alzheimer's	pCMVSPORT 3.0	LP015
HKBA	Ku 812F Basophils Line	pSport 1	LP015
HS2S	Saos2, Dexamethosone Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
HTFM	TF-1 Cell Line GM-CSF Treated	pSport 1	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport 1	LP016
HEAH	Ea.hy.926 cell line	pSport 1	LP016
HINA	Adenocarcinoma Human	pSport 1	LP016
HRMA	Lung Mesothelium	pSport 1	LP016
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport 1	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020
HPSN	Sinus Piniiformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport 1	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
HOCT	Colon Tumor	pSport 1	LP020
HTNT	Tongue Tumour	pSport 1	LP020
HLXN	Larynx Normal	pSport 1	LP020
HLXT	Larynx Tumour	pSport 1	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport 1	LP020
HTNG	Tongue Normal	pSport 1	LP020
HZAA	Thyroid Normal (SDCA2 No)	pSport 1	LP020
HWES	Thyroid Thyroiditis	pSport 1	LP020
HFHD	Ficoll Human Stromal Cells, 5Fu treated	pTrip1Ex2	LP021
HFHM,HFHN	Ficoll Human Stromal Cells, Untreated	pTrip1Ex2	LP021
HPCI	Hep G2 Cells, lambda library	lambda Zap-CMV XR	LP021
HBCA,HBCB,HBCC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORT1	LP022
HDMA, HDMB	CD40 activated monocyte dendritic cells	pSPORT1	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR	Hep G2 Cells, PCR library	lambda Zap-CMV XR	LP022
HAAA, HAAB, HAAC	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPA, HIPB, HIPC	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	pSPORT1	LP022
HOOH, HOOI	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low	pSPORT1	LP022

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	Malignant Pot		
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA.HUJB.HUJC.HUJD.HUJE	B-Cells	pCMVSPORT 3.0	LP022
HNOA.HNOB.HNOC.HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022
HNLM	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORT1	LP022
HUUA.HUUB.HUUC.HUUD	B-cells (unstimulated)	pTriplEx2	LP022
HWWA.HWWB.HWWC.HWWD,HWE.HWWF.HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSPORT 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport 1	LP023
HPCO HPCP HPCQ HPCT	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
HOCM HOCO HOCQ HOCQ	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport 1	LP023
HCBM HCBN HCBO	Breast, Cancer: (4004943 A5)	pSport 1	LP023
HNBH HNBV HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
HBCP HBCQ	Breast, Cancer: (4005522 A2)	pSport 1	LP023
HBCI	Breast, Cancer: (9806C012R)	pSport 1	LP023
HSAM HSAN	Stromal cells 3.88	pSport 1	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport 1	LP023
HSCA HSEN HSEO	Stromal cells (HBM3.18)	pSport 1	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport 1	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport 1	LP023
HCOM HCON HCOO HCOP HCOQ	Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023
HBNM	Breast, Cancer: (9802C020E)	pSport 1	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport 1	LP023

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 5. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

5 Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with  $^{32}\text{P}$ - $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid  
10 mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using  
15 Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the  
20 nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu\text{l}$  of reaction mixture with 0.5  $\mu\text{g}$  of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $\text{MgCl}_2$ , 0.01% (w/v) gelatin, 20  $\mu\text{M}$  each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of  
25 Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR  
30 product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not



limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

5 Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full  
10 length gene.

This above method starts with total RNA isolated from the desired source, although poly-A<sup>+</sup> RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the  
15 RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis  
20 using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

#### 25 *Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide*

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X, according to the method  
30 described in Example 1. (See also, Sambrook.)

*Example 3: Tissue specific expression analysis*

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which show tissue specific expression are selected.

The original clone from which the specific EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Schuell) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

*Example 4: Chromosomal Mapping of the Polynucleotides*

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute

cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR  
5 fragment in the particular somatic cell hybrid.

***Example 5: Bacterial Expression of a Polypeptide***

A polynucleotide encoding a polypeptide of the present invention is amplified using  
10 PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial  
15 expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is  
20 ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is  
25 isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto  
30 pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction

sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express  
5 protein in a bacterial system.

***Example 6: Purification of a Polypeptide from an Inclusion Body***

The following alternative method can be used to purify a polypeptide expressed in *E. coli*  
10 when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell  
15 paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then  
20 mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is  
25 discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous  
30 stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16  $\mu$ m membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column  
5 is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of  
10 water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging  
15 from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from  
20 Commassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### *Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System*

25

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of  
30 the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under

control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

5 Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

10 Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard  
15 methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with  
20 appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

25 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the  
30 cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA",

Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu\text{g}$  of BaculoGold™ virus DNA and 5  $\mu\text{g}$  of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu\text{l}$  of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu\text{l}$  Lipofectin plus 90  $\mu\text{l}$  Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200  $\mu\text{l}$  of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5  $\mu\text{Ci}$  of  $^{35}\text{S}$ -methionine and 5  $\mu\text{Ci}$   $^{35}\text{S}$ -cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.



*Example 8: Expression of a Polypeptide in Mammalian Cells*

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used

for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five  $\mu$ g of the expression plasmid pC6 or pC4 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10,

25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well  
5 plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

10 *Example 9: Protein Fusions*

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding  
15 protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion  
20 proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

25 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be  
30 ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the

vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

10 GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGCCCAG  
CACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAACCCAAGGA  
CACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC  
CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT  
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC  
15 AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC  
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAGCC  
AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG  
CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC  
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGAC  
20 CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACC  
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT  
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT  
GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:837)

25 *Example 10: Production of an Antibody from a Polypeptide*

#### a) Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide

of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide of the present invention are prepared  
5 using hybridoma technology. (Kohler et al., *Nature* 256:495 (1975); Kohler et al., *Eur. J. Immunol.* 6:511 (1976); Kohler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-  
10 expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell  
15 line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981)). The hybridoma cells obtained through such a  
20 selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is  
25 possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the  
30 present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

10 **b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs**

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

*Rescue of the Library.* A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10<sup>8</sup> TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra

8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10<sup>13</sup> transducing units/ml (ampicillin-resistant clones).

*Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10<sup>13</sup> TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

*Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 µg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

*Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide*

RNA isolated from entire families or individual patients presenting with a phenotype  
5 of interest (such as a disease) is be isolated. cDNA is then generated from these RNA  
samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a  
template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X;  
and/or the nucleotide sequence of the related cDNA in the cDNA clone contained in a  
deposited library. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30  
10 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using  
buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4  
polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The  
intron-exon borders of selected exons is also determined and genomic PCR products  
15 analyzed to confirm the results. PCR products harboring suspected mutations is then cloned  
and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic  
Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States  
Biochemical). Affected individuals are identified by mutations not present in unaffected  
20 individuals.

Genomic rearrangements are also observed as a method of determining alterations in  
a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2  
are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim),  
and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991).  
25 Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA  
for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium  
iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are  
obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination  
30 with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable  
excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image



collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

*Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample*

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

*Example 13: Formulation*

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed  
5 herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good  
10 medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

15 As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given  
20 continuously, the Therapeutic is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

25 Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of  
30 administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray.

5 "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

10 Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

15 Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers* 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., *Id.*) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

20 Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (see generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci.(USA)* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being  
30 adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987);

Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated  
5 generally by mixing it at the desired degree of purity, in a unit dosage injectable form  
(solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that  
is non-toxic to recipients at the dosages and concentrations employed and is compatible with  
other ingredients of the formulation. For example, the formulation preferably does not  
include oxidizing agents and other compounds that are known to be deleterious to the  
10 Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and  
intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the  
product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier,  
more preferably a solution that is isotonic with the blood of the recipient. Examples of such  
15 carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous  
vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that  
enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the  
dosages and concentrations employed, and include buffers such as phosphate, citrate,  
20 succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic  
acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or  
tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic  
polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic  
acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including  
25 cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA;  
sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic  
surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about  
0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be  
30 understood that the use of certain of the foregoing excipients, carriers, or stabilizers will  
result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is

readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

5           Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic  
10       using bacteriostatic Water-for-Injection.

          The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products,  
15       which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

          The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention  
20       include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include,  
25       but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping  
30       cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or

concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate  
5 administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories,  
10 conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous  
15 lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited  
20 to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO  
25 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7  
30 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or

prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection.

In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone,



azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine);

cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol  
5 diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, Therapeutics of the invention are administered in  
10 combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

In an additional embodiment, the Therapeutics of the invention are administered in  
15 combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not  
20 limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth  
25 Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors,  
30 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2

(VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO  
5 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

10 In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

15 In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

20 In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

*Example 14: Method of Treating Decreased Levels of the Polypeptide*

25 The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual can be treated by administering the  
30 agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or

antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

5

*Example 15: Method of Treating Increased Levels of the Polypeptide*

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to  
10 such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

15 For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

20 *Example 16: Method of Treatment Using Gene Therapy-Ex Vivo*

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces.  
25 Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated  
30 at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer

is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on  
5 agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a  
10 HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the  
15 gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce  
20 infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer  
25 cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his.  
30 Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after

having been grown to confluence on cytodex 3 microcarrier beads.

*Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention*

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Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; 10 International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting 15 sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct 20 restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the 25 appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

30 In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral

particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na<sub>2</sub>HPO<sub>4</sub>, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately  $3 \times 10^6$  cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately  $1.5 \times 10^6$  cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V,

respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

*Example 18: Method of Treatment Using Gene Therapy - In Vivo*

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell,



including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will

appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

#### *Example 19: Transgenic Animals*

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (*see, e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campbell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci.

USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

5

*Example 20: Knock-Out Animals*

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

25

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding

30

sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

*Example 22: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation*

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a

positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15.

5 Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands  
10 CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the  
15 detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

**In Vitro Assay-** Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention  
20 on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell  
25 proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to  
30 which are added  $10^5$  B-cells suspended in culture medium (RPMI 1640 containing 10% FBS,  $5 \times 10^{-5}$ M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and  $10^{-5}$  dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well)

with  $^3\text{H}$ -thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

**In Vivo Assay-** BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

#### *Example 23: T Cell Proliferation Assay*

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of  $^3\text{H}$ -thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100  $\mu\text{l}$ /well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1  $\mu\text{g}/\text{ml}$  in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells ( $5 \times 10^4$ /well) of mAb coated plates



in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200  $\mu$ l). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100  $\mu$ l of supernatant is removed and stored -20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100  $\mu$ l of medium containing 0.5  $\mu$ Ci of  $^3$ H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of  $^3$ H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 24: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells*

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- $\alpha$ , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC $\gamma$ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow

cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly  
5 influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells ( $10^6$ /ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using  
10 commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules,  
15 molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

20 FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are  
25 analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine  
30 whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified

from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

- 5 Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in  
10 polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of  $2 \times 10^6$ /ml in PBS containing PI at a final concentration of 5  $\mu$ g/ml, and then incubated at room temperature for 5 minutes before FACSscan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in  
15 this experimental paradigm.

- Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows.  
20 Human monocytes are incubated at a density of  $5 \times 10^5$  cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use.  
25 Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

- Oxidative burst. Purified monocytes are plated in 96-w plate at  $2 \times 10^5$  cell/well. Increasing  
30 concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To

the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The  
5 absorbance is read at 610 nm. To calculate the amount of H<sub>2</sub>O<sub>2</sub> produced by the macrophages, a standard curve of a H<sub>2</sub>O<sub>2</sub> solution of known molarity is performed for each experiment.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test  
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 25: Biological Effects of Agonists or Antagonists of the Invention*

15 Astrocyte and Neuronal Assays.

Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for  
20 the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on  
25 cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not  
30 necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal

culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

5 Fibroblast and endothelial cell assays.

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate  
10 for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE<sub>2</sub> assays,  
15 the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for PGE<sub>2</sub> by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one  
20 day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1 $\alpha$  for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on  
25 growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of  
30 striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection

neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine ( $MPP^+$ ) and released. Subsequently,  $MPP^+$  is actively accumulated in  
5 dopaminergic neurons by the high-affinity reuptake transporter for dopamine.  $MPP^+$  is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has  
10 trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, agonists or antagonists of the invention can be  
15 evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined *in vitro* in a  
20 dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm<sup>2</sup> on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with  
25 paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a  
30 developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*.

Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 26: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells*

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at  $2.5 \times 10^4$  cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

*Example 27: Rat Corneal Wound Healing Model*

This animal model shows the effect of an agonist or antagonist of the invention on neovascularization. The experimental protocol includes:

- a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.
- b) Inserting a spatula below the lip of the incision facing the outer corner of the

eye.

c) Making a pocket (its base is 1-1.5 mm from the edge of the eye).

d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.

5 e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test  
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 28: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models*

*A. Diabetic db+/db+ Mouse Model.*

15 To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner,  
20 M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal  
25 recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-  
30 55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*,



*Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

5       The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The  
10   animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

15       Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical  
20   area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with  
25   sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no  
30   longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups

received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue

control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

- 5 Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

#### *B. Steroid Impaired Rat Model*

- The inhibition of wound healing by steroids has been well documented in various *in vitro* and  
10 *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahlet *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*,  
15 *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish  
20 phenomenon in rats (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

- To demonstrate that an agonist or antagonist of the invention can accelerate the  
25 healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

- Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are  
30 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All

manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm<sup>2</sup>, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned  
5 perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine  
hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds.  
Histologic examination of the wounds allows assessment of whether the healing process and  
the morphologic appearance of the repaired skin is improved by treatment with an agonist or  
antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to  
10 determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is  
considered significant.

The studies described in this example tested activity of agonists or antagonists of the  
invention. However, one skilled in the art could easily modify the exemplified studies to test  
15 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 29: Lymphadema Animal Model*

The purpose of this experimental approach is to create an appropriate and consistent  
20 lymphedema model for testing the therapeutic effects of an agonist or antagonist of the  
invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in  
the rat hind limb. Effectiveness is measured by swelling volume of the affected limb,  
quantification of the amount of lymphatic vasculature, total blood plasma protein, and  
histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly,  
25 the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis.  
Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the  
right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in  
70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric  
30 measurements are made prior to injecting dye into paws after marking 2 measurement levels  
(0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left  
paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric

measurements are then made following injection of dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel  
5 that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and  
10 ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of  
15 ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the  
20 intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

25 Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with  
30 Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped

into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca<sup>2+</sup> comparison.

5       Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quilltine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

10       Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test  
15 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 30: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention*

20       The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial  
25 leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

30       Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of an agonist or antagonist of the invention to mediate a suppression of TNF- $\alpha$  induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- $\alpha$  treated ECs when co-stimulated with a member of the FGF family of proteins.

5 To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO<sub>2</sub>. HUVECs are seeded in 96-well plates at concentrations of  $1 \times 10^4$  cells/well in EGM medium at 37 degree C for 18-24 hrs or  
10 until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well  
15 plate to confluence. Growth medium is removed from the cells and replaced with 90  $\mu$ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10  $\mu$ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca<sup>++</sup> and Mg<sup>++</sup>) is added  
20 to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10  $\mu$ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1  
25 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20  $\mu$ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH  
30 10.4). 100  $\mu$ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer:  $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$ . 5  $\mu$ l of each dilution is added to triplicate



wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPN reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on  
5 blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test  
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

*Example 31: Production Of Polypeptide of the Invention For High-Throughput Screening Assays*

15 The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 33-42.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working  
20 solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for  
25 up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

30 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing

a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add  
5 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then  
10 person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with  
15 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>-5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>-9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>-7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>-H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; .4320 mg/L of ZnSO<sub>4</sub>-7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-  
20 Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L- Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56  
25 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L- Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L- Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22  
30 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; and 99.65 mg/ml of L-

Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

#### *Example 32: Construction of GAS Reporter Construct*

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements

alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class 1, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:838)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

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		<u>JAKs</u>			<u>STATS GAS(elements) or ISRE</u>	
	<u>Ligand</u>	<u>tyk2</u>	<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	
<u>IFN family</u>						
5	IFN-a/B	+	+	-	-	1,2,3 ISRE
	IFN-g		+	+	-	1 GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3
<u>gp130 family</u>						
10	IL-6 (Pleiotrohic)	+	+	+	?	1,3 GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotrohic)	?	+	?	?	1,3
	OnM(Pleiotrohic)	?	+	+	?	1,3
	LIF(Pleiotrohic)	?	+	+	?	1,3
	CNTF(Pleiotrohic)	-/+	+	+	?	1,3
15	G-CSF(Pleiotrohic)	?	+	?	?	1,3
	IL-12(Pleiotrohic)	+	-	+	+	1,3
<u>g-C family</u>						
	IL-2 (lymphocytes)	-	+	-	+	1,3,5 GAS
20	IL-4 (lymph/myeloid)	-	+	-	+	6 GAS (IRF1 = IFP
	>>Ly6)(IgH)					
	IL-7 (lymphocytes)	-	+	-	+	5 GAS
	IL-9 (lymphocytes)	-	+	-	+	5 GAS
	IL-13 (lymphocyte)	-	+	?	?	6 GAS
25	IL-15	?	+	?	+	5 GAS
<u>gp140 family</u>						
	IL-3 (myeloid)	-	-	+	-	5 GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5 GAS
30	GM-CSF (myeloid)	-	-	+	-	5 GAS
<u>Growth hormone family</u>						
	GH	?	-	+	-	5
	PRL	?	+/-	+	-	1,3,5
35	EPO	?	-	+	-	5 GAS(B-

CAS&gt;IRF1=IFP&gt;&gt;Ly6)

Receptor Tyrosine Kinases

	EGF	?	+	+	-	1,3	GAS (IRF1)
5	PDGF	?	+	+	-	1,3	
	CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

10 5':GCGCCTCGAGATTTCCCGAAATCTAGATTTCCCGAAATGATTTCCCG  
GAAATGATTTCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:839)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:840)

15 PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

20 5':CTCGAGATTTCCCGAAATCTAGATTTCCCGAAATGATTTCCCGAAA  
TGATTTCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCG  
CCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCT  
CCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCC  
TCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTA  
25 GGCTTTTGCAAAAAAGCTT:3' (SEQ ID NO:841)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

*Example 33: High-Throughput Screening Assay for T-cell Activity.*

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the



GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC  
5 Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4<sup>+</sup> Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately  
10 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells  
15 containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

20 During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

25 The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

30 On the day of treatment with the supernatant, the cells should be washed and

resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

5        Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

      After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12  
10    channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

      The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul  
15    samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

20        As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

      The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

25

*Example 34: High-Throughput Screening Assay Identifying Myeloid Activity*

      The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention  
30    proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using

the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

- 5 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml  
10 penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at 37 degrees C for 45 min.

- 15 Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

- 20 These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

- Add 50 ul of the supernatant prepared by the protocol described in Example  
25 31. Incubate at 37 degree C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

- 30 *Example 35: High-Throughput Screening Assay Identifying Neuronal Activity.*

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:842)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:843)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and

allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and  
5 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by  
10 growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS  
15 (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$   
20 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over  
25 fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

*Example 36: High-Throughput Screening Assay for T-cell Activity*

30 NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide

variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class I MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:844), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC  
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:845)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:840)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC  
5 ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA  
CTAATTTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTA  
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA  
GCTT:3' (SEQ ID NO:846)

Next, replace the SV40 minimal promoter element present in the pSEAP2-  
10 promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and  
HindIII. However, this vector does not contain a neomycin resistance gene, and  
therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP  
cassette is removed from the above NF-KB/SEAP vector using restriction enzymes  
15 SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly,  
the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the  
GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are  
created and maintained according to the protocol described in Example 33. Similarly,  
20 the method for assaying supernatants with these stable Jurkat T-cells is also described  
in Example 33. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to  
wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### *Example 37: Assay for SEAP Activity*

25

As a reporter molecule for the assays described in Examples 33-36, SEAP  
activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the  
following general procedure. The Tropix Phospho-light Kit supplies the Dilution,  
Assay, and Reaction Buffers used below.

30

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x

dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

- Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

#### Reaction Buffer Formulation:

15

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25



24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

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*Example 38: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability*

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants  
5 which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to  
10 measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star  
15 black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To  
load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate  
20 is incubated at 37 degrees C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to  $2-5 \times 10^6$  cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension.  
25 The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to  $1 \times 10^6$  cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

30 For a non-cell based assay, each well contains a fluorescent molecule, such as

fluor-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular  $\text{Ca}^{++}$  concentration.

*Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity*

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol

is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4

degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

5        Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for  
10 a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>,  
15 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

20        Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-  
25 POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound  
30 peroxidase activity is quantitated using an ELISA reader and reflects the level of

tyrosine kinase activity.

*Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity*

5        As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other  
10        molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA  
15        plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody  
20        detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants  
25        obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit)  
30        antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the

Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased  
5 fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

*Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation*

10 This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond.  
15 Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in  
20 such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or  
25 agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells  
30 are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-

glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to  $2.5 \times 10^5$  cells/ml. During this time, 100  $\mu$ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that  
5 can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10  $\mu$ l of prepared cytokines, 50  $\mu$ l of the supernatants prepared in Example 31 (supernatants at 1:2 dilution = 50  $\mu$ l) and 20  $\mu$ l of diluted cells are added to the media  
10 which is already present in the wells to allow for a final total volume of 100  $\mu$ l. The plates are then placed in a 37°C/5% CO<sub>2</sub> incubator for five days.

Eighteen hours before the assay is harvested, 0.5  $\mu$ Ci/well of [3H] Thymidine is added in a 10  $\mu$ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat  
15 using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60  $\mu$ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined  
20 via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene  
25 therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell  
30 proliferation and/or to decrease the inhibition of cell proliferation in the presence of



cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and  
5 "Infectious Disease" sections above, and elsewhere herein.

*Example 43: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)*

10 The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from  
15 the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein  
20 fibronectin (fn). Adhesion of cells to fn is mediated by the  $\alpha_5\beta_1$  and  $\alpha_4\beta_1$  integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

25 Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of  $0.2 \mu\text{g}/\text{cm}^2$ . Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem

cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10%  
5 of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment ( 5% CO<sub>2</sub>, 7% O<sub>2</sub>, and 88% N<sub>2</sub> ) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be  
10 accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

15 If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and  
20 elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the  
25 proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

30 Moreover, polynucleotides and polypeptides corresponding to the gene of

interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

*Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation*

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF $\alpha$  stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100  $\mu$ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5  $\mu$ g/ml hEGF, 5mg/ml insulin, 1 $\mu$ g/ml hFGF, 50mg/ml gentamycin, 50  $\mu$ g/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50 $\mu$ g/ml Amphotericin B, 0.4% FBS. Incubate at 37°C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNF $\alpha$  is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides  
5 of the present invention and incubate at 37°C/5% CO<sub>2</sub> until day 5.

Transfer 60 $\mu$ l from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100  $\mu$ l in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the  
10 culture volume (10 $\mu$ l). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100  $\mu$ l/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON  
15 at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200  $\mu$ l/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50  $\mu$ l/well of  
20 diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100  $\mu$ l/well. Cover the plate and incubate 1 h at RT.  
25 Plates are again washed with wash buffer and blotted on paper towels. Add 100  $\mu$ l/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the  
30 polypeptide of the present invention may be involved in dermal fibroblast

proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

*Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells*

5       The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1  
10 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor  
15 participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100  $\mu$ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the  
20 plate in triplicate (in 10  $\mu$ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100  $\mu$ l of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA  
25 and drained. 10  $\mu$ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10  $\mu$ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20  $\mu$ l of diluted ExtrAvidin-Alkaline  
30 Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to

each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 ( $10^0$ ) >  $10^{-0.5}$  >  $10^{-1}$  >  $10^{-1.5}$ . 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [ 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

15 *Example 46: Alamar Blue Endothelial Cells Proliferation Assay*

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with

GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM ) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days.

- 5 After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

- 10 Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and
- 15 inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

20

*Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction*

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides).

- 25 Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and



natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM<sup>®</sup>, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to  $2 \times 10^6$  cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to  $2 \times 10^5$  cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50  $\mu$ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1  $\mu$ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10  $\mu$ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO<sub>2</sub>, and 1  $\mu$ C of [<sup>3</sup>H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

- 5       The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both
- 10   incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of Serial No. 60/124,270 are also incorporated herein by reference in their entireties.

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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

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Date of deposit <u>20 May 1997</u>	Accession Number <u>209059</u>
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**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

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**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

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The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

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#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Date of deposit <u>20 May 1997</u>	Accession Number <u>209060</u>
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The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

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The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

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Date of deposit <u>20 May 1997</u>	Accession Number <u>209061</u>
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**NORWAY**

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**UNITED KINGDOM**

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ATCC Deposit No. 209061

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

420

Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p>American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) <p>10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p>	
Date of deposit <p>20 May 1997</p>	Accession Number <p>209062</p>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<b>For receiving Office use only</b> <input checked="" type="checkbox"/> This sheet was received with the international application <b>RO/US 08 MAR 2000</b> Authorized officer <b>Yolanda Harrod</b> <b>PCT/Internat'l Appl Processing Div.</b> <b>(703) 305-2870</b>	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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**ATCC Deposit No. 209062****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209062

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

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#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application i
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209063</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
<b>RO/US</b> <b>20 MAR 2000</b> Authorized officer <b>Yolanda Harrod</b> <b>PCT/Int'l Appl Processing Ctr.</b> <b>(703) 305-3670</b>	Authorized officer

**ATCC Deposit No. 209063**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection. the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



Page 2

ATCC Deposit No. 209063

#### DENMARK

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#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>20 May 1997</u>	Accession Number <u>209064</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
<b>RO/US 09 MAR 2000</b>	
Authorized officer <u>Yolanda Harrod</u> PCT/Internat'l Appl Processing Div.	Authorized officer

**ATCC Deposit No. 209064**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209064

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209065
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application RO/US 03 MAR 2000 Authorized officer: <u>Sianda Harroa</u> PCT/International Appl Processing Div. (703) 305-3870	<input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on: Authorized officer: _____
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**ATCC Deposit No. 209065****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**AUSTRALIA**

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**FINLAND**

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**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209065

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

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**NETHERLANDS**

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432

Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209066
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
<b>RO/US</b> <b>03 MAR 2000</b> Authorized officer: Valerie Harrod PCT/Int'l Appl Processing Div. (703) 305-3870	Authorized officer



**ATCC Deposit No. 209066****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

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**AUSTRALIA**

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**FINLAND**

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**UNITED KINGDOM**

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Page 2

ATCC Deposit No. 209066

**DENMARK**

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435

Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution  American Type Culture Collection	
Address of depositary institution (including postal code and country)  10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit  20 May 1997	Accession Number  209067
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
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Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. (200) 305-3670

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<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer

**ATCC Deposit No. 209067****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209067

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <b>American Type Culture Collection</b>	
Address of depositary institution (including postal code and country) <b>10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</b>	
Date of deposit <b>20 May 1997</b>	Accession Number <b>209068</b>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application <b>RO/US 03 MAR 2000</b> Authorized officer <b>Yolanda Harrod</b> <b>PCT/Internat'l Appl Processing Div.</b> <b>(703) 305 3870</b>	<input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on: Authorized officer
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**ATCC Deposit No. 209068****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209068

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



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Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 20 May 1997	Accession Number 209069
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer PCT/Int'l App. Processing Div. (703) 305-3879	Authorized officer

**ATCC Deposit No. 209069****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209069

#### **DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### **SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### **NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT <span style="float: right;">Further deposits are identified on an additional sheet <input type="checkbox"/></span>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) <p style="text-align: center;">10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p>	
Date of deposit <p style="text-align: center;">12 January 1998</p>	Accession Number <p style="text-align: center;">209579</p>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) <span style="float: right;">This information is continued on an additional sheet <input type="checkbox"/></span>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application
Authorized officer <p style="text-align: center;">MAR 2000</p>

For International Bureau use only
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Authorized officer

**ATCC Deposit No. 209579**

**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209579

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution  American Type Culture Collection	
Address of depositary institution (including postal code and country)  10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit  12 January 1998	Accession Number  209578
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application <b>RO/US 03 MAR 2000</b> Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. <b>(703) 305-3870</b>	<input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on:  Authorized officer
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**ATCC Deposit No. 209578****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



Page 2

ATCC Deposit No. 209578

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution  American Type Culture Collection	
Address of depositary institution (including postal code and country)  10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit  16 July 1998	Accession Number  203067
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")          	

<b>For receiving Office use only</b> <input checked="" type="checkbox"/> This sheet was received with the international application <b>RO/US 03 MAR 2000</b> Authorized officer J. A. Harrod PCT Internat'l Appl Processing Ctr 703 305-3870	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer
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**ATCC Deposit No. 203067****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2  
ATCC Deposit No. 203067

#### DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

#### SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

#### NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

453

Applicant's or agent's file reference number	PA103PCT	International application*
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT	
Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 July 1998	Accession Number 203068
C. ADDITIONAL INDICATIONS (leave blank if not applicable)	
This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<b>RO/US 08 MAR 2000</b>
Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div.

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<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer

**ATCC Deposit No. 203068****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203068

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application ?
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution  American Type Culture Collection	
Address of depositary institution (including postal code and country)  10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit  1 February 1999	Accession Number  203609
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")          	

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**ATCC Deposit No. 203609****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203609

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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Applicant's or agent's file reference number	PA103PCT	International application n°
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p>	
Address of depositary institution (including postal code and country) <p style="text-align: center;">10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p>	
Date of deposit <p style="text-align: center;">1 February 1999</p>	Accession Number <p style="text-align: center;">203610</p>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")     	

<b>For receiving Office use only</b> <input checked="" type="checkbox"/> This sheet was received with the international application <b>RO/US 06 MAR 2000</b> Authorized officer <u>Volanda Harrod</u> <b>PCT/International Appl Processing Div.</b> <b>(703) 305-3670</b>	<b>For International Bureau use only</b> <input type="checkbox"/> This sheet was received by the International Bureau on:  Authorized officer _____
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**ATCC Deposit No. 203610****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203610

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

462

Applicant's or agent's file reference number	PA103PCT	International application?
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution  American Type Culture Collection	
Address of depositary institution (including postal code and country)  10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit  17 November 1998	Accession Number  203485
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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RO/US 08 MAR 2000	
Authorized officer Yolanda Harrod PCT Admin / Appl Processing Unit (703) 305-3670	Authorized officer

**ATCC Deposit No. 203485****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203485

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by an applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.



465

Applicant's or agent's file reference number	PA103PCT	International application number
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 18 June 1999	Accession Number PTA-252
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<b>RO/US 03 MAR 2000</b>
Authorized officer Yolanda Harrod PCT/Int'l Appl Processing Div.

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Authorized officer

**ATCC Deposit No. PTA-252****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

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**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. PTA-252

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

468

Applicant's or agent's file reference number	PA103PCT	International application No.
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <b>American Type Culture Collection</b>	
Address of depositary institution (including postal code and country) <b>10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</b>	
Date of deposit <b>18 June 1999</b>	Accession Number <b>PTA-253</b>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application <b>RO/US 03 MAR 2000</b> Authorized officer <b>Volanda Harrod</b> <b>PCT/Internat'l Appl Processing Div.</b> <b>(703) 305-3670</b>	<input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on: Authorized officer
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**ATCC Deposit No. PTA-253****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

**Page 2****ATCC Deposit No. PTA-253****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

471

Applicant's or agent's file reference number	PA103PCT	International application?
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## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution  American Type Culture Collection	
Address of depositary institution (including postal code and country)  10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit  22 December 1999	Accession Number  PTA-1081
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input type="checkbox"/> This sheet was received by the International Bureau on:
RO/US 03 MAR 2000 Authorized <u>Yolanda Harrod</u> PCT/Intemat'l Appl Processing Div. (703) 305-3670	Authorized officer

**ATCC Deposit No. PTA-1081****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

**NORWAY**

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

**AUSTRALIA**

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

**FINLAND**

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.



Page 2

ATCC Deposit No. PTA-1081

**DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

**SWEDEN**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

**NETHERLANDS**

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

*What Is Claimed Is:*

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
- 5 (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
- 10 (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
- (c) a polynucleotide encoding a polypeptide fragment of a polypeptide encoded by SEQ ID NO:X or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
- 15 (d) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
- (e) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
- 20 (f) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X, having biological activity;
- (g) a polynucleotide which is a variant of SEQ ID NO:X;
- 25 (h) a polynucleotide which is an allelic variant of SEQ ID NO:X;
- (i) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
- (j) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i), wherein said polynucleotide does not
- 30 hybridize under stringent conditions to a nucleic acid molecule having a nucleotide

sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

5

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

10

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

15

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

20

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

25

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.
11. An isolated polypeptide comprising an amino acid sequence at least  
5 95% identical to a sequence selected from the group consisting of:
- (a) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
  - (b) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone, having biological activity;
  - 10 (c) a polypeptide domain of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
  - (d) a polypeptide epitope of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
  - (e) a full length protein of SEQ ID NO:Y or of the sequence encoded by the  
15 cDNA included in the related cDNA clone;
  - (f) a variant of SEQ ID NO:Y;
  - (g) an allelic variant of SEQ ID NO:Y; or
  - (h) a species homologue of the SEQ ID NO:Y.
- 20 12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
- 25 13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
- 30 15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

5           16.    The polypeptide produced by claim 15.

17.    A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

10

18.    A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

15           (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19.    A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

20           (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

25           20.    A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

30

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.
22. A method of identifying an activity in a biological assay, wherein the method comprises:
  - 5 (a) expressing SEQ ID NO:X in a cell;
  - (b) isolating the supernatant;
  - (c) detecting an activity in a biological assay; and
  - (d) identifying the protein in the supernatant having the activity.
- 10 23. The product produced by the method of claim 20.

## SEQUENCE LISTING

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&lt;210&gt; 6

&lt;211&gt; 1196

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
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<222> (157)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (998)  
<223> n equals a,t,g, or c

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<210> 7  
<211> 624  
<212> DNA  
<213> Homo sapiens

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c 301

<210> 9  
<211> 686  
<212> DNA  
<213> Homo sapiens

<400> 9  
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<210> 10  
<211> 397  
<212> DNA  
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<220>  
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<222> (379)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (394)  
<223> n equals a,t,g, or c

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agtgagcatc tctggcttgg gggaggctgc tcattaagtg cctgcctgcc cgscamccc 300  
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<210> 11

<211> 563

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (37)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (510)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (562)

<223> n equals a,t,g, or c

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<211> 443  
<212> DNA  
<213> Homo sapiens

<400> 12  
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<211> 2438  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (117)  
<223> n equals a,t,g, or c

<220>  
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<222> (681)  
<223> n equals a,t,g, or c

<220>  
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<222> (713)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2413)  
<223> n equals a,t,g, or c

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&lt;210&gt; 14

&lt;211&gt; 2347

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 14

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&lt;210&gt; 15

&lt;211&gt; 2006

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (862)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1006)

&lt;223&gt; n equals a,t,g, or c

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<212> DNA

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<220>

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<222> (613)

<223> n equals a,t,g, or c

<220>

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<222> (932)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (933)

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<220>

<221> misc feature

<222> (985)

<223> n equals a,t,g, or c

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gactgtccct gcatcccatc tccaacaggg aacagcttct ggctcctcca aagcagtctc 720
cactgttggt gtgactacag ctccgtctcc taaacaggca cctgagcaac aatgattatg 780
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gagttgcatc attgttttaa gctgcctggt caaggcagcc aggcgagggt gatggcaacg 900
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<210> 17

<211> 1589

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (25)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (555)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1033)

<223> n equals a,t,g, or c

<400> 17

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tgccccccac cccagcctaa gatgaagagg atcgaggctt tgctcagagct gggaggggtt 120
ttcgaagctc agcccacccc cctcattttg gatataggct agtgaaggcc caggagagag 180
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ccatgattcg cccaaagcca gacagcaacg gggaggccra gtgcaggctg gcaccgcctt 240
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gggaaatggc ttgaagccaa gtcagcttg cctccacgc tgtctccaga cccccacccc 360
ttccccactg cctgccacc cgtggagatg ggatgcttgc ctagggcctg gtccatgatg 420
gagtcagggtt tggggttcgt ggaaagggtg ctgcttcct ctgctgtcm ctctcaggca 480
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agaaagaaaa ataaaaaaaa aaaaaaaaaa 1589

```

&lt;210&gt; 18

&lt;211&gt; 846

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (746)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 18

```

gcacccgcct cgcccgatg gccaccgcag acccagtcct ccggggcagcc ggcccagccc 60
gcgcccctgg tgccactgca ccagaagcag agccgcacat ccccatcca gaagccgcgg 120
ggcstcgacc ctgtggagat cctgcaggag cgcgagtaca ggctgcaggc tcgcatcgca 180
caccgaattc aggaacttga aaaccttccc gggctccctgg ccggggattt gcgaacccaa 240
gcgaccattg agctcaaggc cctcaggctg ctgaacttcc agaggcagct gcgccaggag 300
gtggtggtgt gcatgcggag ggacacagcg ctggagacag ccctcaatgc taaggcctac 360
aagcgcasaa gcgccagtcc ctgcgcgagg ccgcacacac tgagaagctg gagaagcagc 420
agaagatcga gcaggagcgc aagcgccggc agaagcacca ggaatacctc aatagcattc 480
tccagcatgc caaggatttc aaggaatatc acagatccgt cacaggcaaa atccagaagc 540
tgaccaaggc agtggccacg taccatgcca acacggagcg ggagcagaag aaagagaacg 600
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acgtggctaa ctcacggagc tgggtgncggc acaaggctgc ccaggctgcc aaggagaaaa 780
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cggatg 846

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<210> 19  
<211> 2192  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (115)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2106)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2118)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2143)  
<223> n equals a,t,g, or c

<400> 19  
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actatacctg aaatgggctc ttgaagagta tctggatgaa tttgaccctt gtcattgccg 180  
gccttgctca aatgtgtggt ttggtactgt tgaggggacc cattgtctgt gccattgcaa 240  
accgtacaca tttgtgtcgg cgtgtgagca aggagtcctc gttagggaatc aagcaggagg 300  
ggttgatgga ggttgagggt gctgtgcctc ttggagcccc tgtgtccaag ggaagaaaac 360  
aagaagccgt gratgcaaka acccacctcc cagtgggggt gggagatcct gcgttgagga 420  
aacgacagaa agcacacaat gcgaagatga ggagctggag cacttgaggt tgcttgaacc 480  
acattgcttt cctttgtctt tggttccaac agaattctgt ccatcacctc ctgccttgaa 540  
agatggattt gttcaagatg aaggtacaat gtttcctgtg gggaaaaatg tagtgtacwc 600  
ttgcaatgaa ggatactctc ttattggaaa ccagtgggc agatgtggag aagatttacg 660  
gtggcttggt ggggaaatgc attgtcagaa aattgcctgt gttctacctg tactgatgga 720  
tggcatacag agtcaccccc aaaaaccttt ctacacagtt ggtgagaagg tgactgtttc 780  
ctgttcaggt ggcattgtcct tagaagggtc ttcagcattt ctctgtggct ccagccttaa 840  
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agtgcctaaa tgtcagcgct gggagaaact gcagaattca agatgtgttt gtaaaatgcc 960  
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tgctgcggaa acccagtagg ctctgtgagg ccmtgggtcag cttgcttgga atccagcagg 1380  
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gcctcccaaa gtgctgggat acagacatga ac 2192
```

&lt;210&gt; 20

&lt;211&gt; 1011

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (54)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 20

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cggggatgga agcgtttttg gggtcgcggt ccggactttg ggcggggggt ccggccccag 120
gacagtttta ccgcattccr tccactcccg attccttcat ggatccggcg tctgcacttt 180
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aggagcttct gggagatgga cacagctata gtcctagagc tattcattca tggtgacca 480
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gctatgctga tggagagagc ttctcgggtt atgtggacat gcttgggtga gcctatgaag 600
ccccttcgct ggccactggt tatgggtgat acttggctca gcctctgctg cgagaagttc 660
tggaagaagca gccagtgcga agccagaccg aggccgcgca cttagtagaa cgctgcatgc 720
gagtgcgtga ctaccagatg gcccgttctt acaaccggtt tcaaategcc actgtcaccg 780
aaaaagggtg tgaaatagag ggaccattgt ctacagagac caactgggat attgccaca 840
tgatcagtg ctttgaatga aatacagatg cattatccag aactgaagtt gcctacttt 900
taactttgaa cttggctagt tcaaagatag actcttcttt tgtaaagtaa ataaattctt 960
caaatgcaa aaaaaaaaaa aaaaaaaaaa cttragact agttctctct c 1011
```

&lt;210&gt; 21

&lt;211&gt; 2019

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2003)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2007)

<223> n equals a,t,g, or c

<400> 21

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acccactggt tttcctctcc catggacaca gtcacagagg ctgggatggc catagcaatg 180
gcgggtgagcc ccatgggggtg tggggggaagg agcaaggact ccatcgccctt tcccaaagg 240
cattcagtcc tgcctctkgt cacttagtag tagtctcttt ttaatcctgt agcttacagg 300
cgggtattggs ttcattccacc acaactgtac amctgaattc caggccaatg aagttyggaa 360
agtgaaggty wgaagggcaa cgatcattag caagcgctcc tgggaattgc actgaggtgg 420
gggtgggggtg gagtagggggt ttattctaat ttagtattct ttcttcccac catgggggttc 480
agttactgag aagaccctga gattctgttt cttaaagcag cagcaataga ccagggtgtac 540
agtgccctcca gcctaccat gtctctaaga tgtgttggtg tgatttggtc ttgtggcact 600
gccaaaggga tcgataagca gagaccccat gcttcagatc aagagcctga tgaaagtagt 660
tcaaagatgc gatgcccttt ctcaccatcc ctttcagaaa atatgaacag ggattcatca 720
cagaccctgt ggtcctcagc cccaaggatc gcgtgcggga tgttttttag gccaaaggccc 780
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gcccagggtg aaggtggcgt ccatagcctc cattcgtatg agaagcggct tttctgaaa 1920
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aaaaaaaaat tctcgggggg ggnccngta cccaattgg 2019
```

<210> 22

<211> 2022

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1588)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1615)

<223> n equals a,t,g, or c

<400> 22

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tgtgacgcca ctacacctta ctgaggtgca cgagggccgt gctgacatca tgatcgactt 180
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gccttcttcc ccaagactca ccgagaaggg gatgtccact tcgactatga tgagacctgg 300
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cagccctgtg gacgctgcct tcgaggatgc ccagggccac atttggttct tccaagggtg 780
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caggccggat cctcctgaag cctttttcgc agcactgcta tctcccaaag ccattgtaaa 1860
tgtgtgtaca gtgtgtataa accttcttct tctttttttt ttttaaaact aggattgtca 1920
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aaaaaaaaaa aaaaagggag gccgctcgcg atctagaact ag 2022
```

<210> 23

<211> 1126

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1126)

<223> n equals a,t,g, or c

<400> 23

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caggtaaaact cctgtccttt acacattcgg ctccctggag cagactctgg tcttctttgg 120
gtaaacgtgt gacgggggaa agccaaggtc tggagaagct ccaggaaca ayygatggcc 180
ttgcagcact cacacaggac ccccttcccc taccctctcc tctctgccgc aatacaggaa 240
ccccagggg aaagatgagc tttcttaggc tacaattttc tcccaggaag ctttgatttt 300
taccgtttct tccctgtatt ttctttctct actttgagga aaccaaagta accttttgca 360
cctgtctctct tgtaatgata tagccagaaa aacgtgttgc cttgaaccac tccctctatc 420
tctcctccaa gacactgtgg acttggtcac cagctcctcc cttgttctct aagttccact 480
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gagtattggg tagatatatt ttctgaatac aaagtgatgt gtttaaatac tgcaattaaa 1080
gtgatactga aacacaaaaa aaaaaaaaaa aaaaaaaan 1126
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<210> 24

<211> 2598

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2304)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2500)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2533)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2553)

<223> n equals a,t,g, or c

<400> 24

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raggtttaa garactacca gaccatttcc caatgaatgt cttggtacca ccagaccctg 120
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agttcctatt gattcatcag attttgcatt ggatattcgc atgcctgggg ttacaccta 180  
acagtccgat acatacttct gcatgtctat gcgaatacca gtggatgagg aagccttcgt 240  
gattgacttc aagcctcgag ccagcatgga tactgtccat cacatgttac tttttggatg 300  
caatatgcct tcatccactg graattactg gttttgtgat gaaggaacct gtacagataa 360  
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&lt;210&gt; 25

&lt;211&gt; 411

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (358)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (368)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (381)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (387)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (392)

<223> n equals a,t,g, or c

<400> 25

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gcacccagat gcccaggcg aggtgcgctt gtctgtaccc ccgctgggtg aggtgatgcg 180
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ctctgagctc caggtcaca tgcacgacac ccggggccgc agtcccccat accagctnng 360
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<210> 26

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (634)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (652)

<223> n equals a,t,g, or c

<400> 26

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cagcccctct tcccttcctc cattgcacat gaacatatgt ccatccatat atattcatca 180
gaatgttaat ttattttgct ccctctgtta ggtccatttt ctaagggtag aagaggcaag 240
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<210> 27

<211> 1903

<212> DNA

<213> Homo sapiens

<400> 27

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<210> 28

<211> 1333

<212> DNA

<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1311)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1313)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1319)  
<223> n equals a,t,g, or c

<400> 28  
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tggccatctt cgggcccccc aacacctact acgagggcgg ctacttcaag gcgcgcctca 180  
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ttctcctgag tgtgatctcc ctctgaacg agcccaacac cttctcgccc gcaaactgtg 420  
acgcctccgt gatgtacagg aagtggaaag agagcaaggg gaaggatcgg gagtacacag 480  
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<210> 29  
<211> 1327  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (573)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1307)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1325)  
<223> n equals a,t,g, or c

<400> 29  
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agcagcgcca gcagatggag cagatgaagc agcgcacgcs ggaggagAAC atcatgaaat 180  
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<210> 30  
<211> 709  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (696)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (701)  
<223> n equals a,t,g, or c

<400> 30

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gtgaaaactt tgatgattat atgaaagaag taggagtgagg ctttgccacc aggaaagtgg 180  
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<210> 31

<211> 1108

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (389)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (397)

<223> n equals a,t,g, or c

<400> 31

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aagaagggtg aggagaagaa gaccaggact atgacttgag ccagctgcag cagcctgaca 180  
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tgcaataaaa gggagttttc atatcacc 1108

<210> 32

<211> 526

<212> DNA  
<213> Homo sapiens  
  
<220>  
<221> misc feature  
<222> (502)  
<223> n equals a,t,g, or c  
  
<220>  
<221> misc feature  
<222> (524)  
<223> n equals a,t,g, or c

<400> 32  
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tgagccagtt attattagag ttgcagaata gaaacttgaa gtgctaaatg gaataatcca 180  
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aaaatttctt tctttcatgg ggcatttgat aatttcagtc tttgacgatt tgtaagccta 420  
gaatatacta agctgaataa cagctctttg gcctcagaat tttccagtag ccagtawttc 480  
yggattaact aagttggaaa cncytattag gaacctccag tggnga 526

<210> 33  
<211> 555  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (494)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (521)  
<223> n equals a,t,g, or c

<400> 33  
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ccctgtctgg cctccaaaac caaaataaaa ctgggtcact ttacaaaaaa aaaaaaaaaa 480  
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<210> 34  
<211> 347  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (288)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (328)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (335)  
<223> n equals a,t,g, or c

<400> 34  
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tgagggccct gtgggtgctg ggcctctcct gctcctgct gaccttcggg tcggtccgar 180  
ctgaygatga agtcgatgtg gatggtacag tggaagagga tctgggtaaa agtagagaag 240  
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ttaaattgcat cccaaataag agaacttnag agagnaagtc cagaaaa 347

<210> 35  
<211> 750  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (701)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (731)  
<223> n equals a,t,g, or c

<400> 35  
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catgggttca acttgacac tgaaaacgca atgaccttcc aagagaacgc aaggggcttc 180  
gggcagagcg tgggtccagct tcagggatcc aggggtggtg ttggagcccc ccaggagata 240  
gtggctgcca accaaagggg cagcctctac cagtgcgact acagcacagg ctcatgcgag 300  
cccatccacc tgcaggtccc cgtggaggcc gtgaacatgt ccctgggcct gtccttgga 360  
gccaccacca gccccctca gctgctggcc tgtggtccca ccgtgcacca gacttgacgt 420



gagaacacgt atgtgaaagg gctctgcttc ctgtttggat ccaacctacg gcagcagccc 480  
cagaagttcc cagaggccct ccgagggtgt cctcaagarg atagtacat tgccttcttg 540  
attgatggct ctggtagcat catcccat gactttcggc ggatgaagga rtttgtctca 600  
actgtgatgg agcaattaaa aaagtccaaa accttgttct ctttgatgca gtactctgaa 660  
gaattccgga ttcactttac ttcaaagagt tccagaacaa ncctaacca agatcactgg 720  
tgaagccaat nacgcagctg cttggggcgg 750

<210> 36

<211> 1291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (298)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (695)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (795)

<223> n equals a,t,g, or c

<400> 36

aagaaaaatg tactacgcct gtcctgtang aagctgaaga tttttgcaat gcccatgcag 60  
gatatacaaga tgatcctgaa aatgggtgcag ctggactcta ttgaagattt gggaagtgc 120  
ttgtacctgg aagctacca ccttggcgaa attttctcct tacctgggcc agatgattaa 180  
tctgcgtaga ctctcctct cccacatcca tgcattctcc tacatttccc cggagaagga 240  
agagcagtat atgcgccagt tcacctctca gttcctcagt ctgcagtgcc tgcagctnct 300  
ctatgtggac tctttatttt tccttagagg ccgcctggat cagtgtctca ggcacgtgat 360  
gaacccttg gaaaccctct caataactaa ctgccggctt tcggaagggg atgtgatgca 420  
tctgtcccag agtcccagcg tcagtcagct aagtgtcctg agtctaagtg gggcatgct 480  
gaccgatgta agtcccagc ccctccaagc tctgctggag agagcctctg ccacctcca 540  
ggacctggtc ttgatgagt gtgggacac ggatgatcag ctcttgccc tctgccttc 600  
ctgagccac tgctccagc ttacaacctt aagcttctac gggaaattcca tctccatate 660  
tgccctgcag agtctcctgc agcacctcat cgggntgagc aatctgacct acgtgctgta 720  
tctgtcccc ctggagagtt atgaggacat ccatggtamc ctccamctg agaggttgc 780  
atctgcatgc caggntcagg gagttgctgt gtgarttggg gcggcccagc atggttctg 840  
cttagtgggc aaccctgtc ctactgtgg ggacagaacc ttctatgacc cggagcccat 900  
cctgtgcccc tgtttcatgc ctaatarctg ggtgcacata tcaaatgctt cattctgcat 960  
acttgacac taaagccagg atgtgcatgc atcttgaagc aacaaagcag ccacagtttc 1020  
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atgttcagtg aggaaaaaaa ggggagttgg ggataggcag atgttgactt grggagktaa 1140  
tgtgatcttt ggggagatac atcttataga gttagaaata gaatctgaat ttctaaaggg 1200  
agawtctggc ttgggaagta catgtaggag ttaatccctg tgtagactgt tgtaaagaaa 1260  
ctgttgaaaa taaagagaag caatgtgaag c 1291

<210> 37

<211> 1535

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1413)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1526)

<223> n equals a,t,g, or c

<400> 37

ggcacgaggg tacgcagagc ttcgtcttcc agcgcaaga gatagcgag ttggcgggc 60  
agtacgctgg gctggaccac gagctggcct tctctcgtct gatcgtggag ctgcgggcg 120  
tgacccagg ccacgtgctg cccgacgagg agctgcagtg ggtgttcgtg aatgcgggtg 180  
gctggatggg cgccatgtgc cttctgcacg cctcgtctgc cgagtatgtg ctgctcttcg 240  
gcaccgcctt gggctcccg gcgcactcgg ggcgctactg ggctgagatc tcggatacca 300  
tcatctctgg caccttccac cagtggagag agggcaccac caaaagtga gtcttctacc 360  
caggggagag ggtagtacac gggcctggtg aggcaacagc tgtggagtgg gggccaaaca 420  
catggatggt ggagtacggc cggggcgctca tcccatccac cctggccttc gcgctggccg 480  
acactgtctt cagcaccag gacttctca cctcttcta tactcttcgc tcctatgctc 540  
ggggcctccg gcttgagctc accacctacc tctttggcca ggacccttga ccagccaggc 600  
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gcccattgtt acagacagg acatacaca tgcagatcct gagtctctgc tgtatgagca 720  
gggatatcca tgcttatgta tccaaacaca gagacccatg ggaacaaatg agacacatat 780  
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ccccgtata ccaagggagc cagtgtgtt cagacacaca catcacagct tgactcacta 900  
actgaggcct ttccatagct ccacagcttc ccacctctc cccaccaaac cggggttcta 960  
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acgagagtaa ttgaagaat gcttgaagtc agcgtcttcc attccagaaa gacccccatt 1260  
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gatctagaca ggtgggcta attccaagg gcccttctg gcctggagaa ggccttttac 1380  
acacacacaa cacatacaca cacacacaca canacacata tcacagttt cacacagccc 1440  
ctgtctgatt ctctgtccat ctgtctgtt ctattaataa agatttgtt atctgttcca 1500  
aaaaaaaaa aaaaaaaaaa aaaaangggg gggct 1535

<210> 38

<211> 295

<212> DNA

<213> Homo sapiens

<400> 38

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ctggtcacac tattacatgc catgcaggca cgcgataaaa cgctggggct ggcaacactg 60
tgcattggcg gcggtcaggg aattgcgatg gtgattgaac ggttgaatta atcaataaaa 120
acacccgata gcgaaagtta tcgggtgttt tcttgaacat cgacggcgaa ggtaacccca 180
ttaatcacca gtcaaaactt ttcaccagcg tcactcgcca gcattacgca tcggtacaat 240
aaatgtttcc tgttttctcat tgaccgatcc ttcacgcgtg atcagcgtca ttggg      295
```

<210> 39

<211> 1300

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (641)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1297)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1298)

<223> n equals a,t,g, or c

<400> 39

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gcggactggc agggggcagg gaagctcaaa gatctggggg gctgccagga aaaagcaaat 60
tctggaagtt aatggttttg agtgattttt aaatccttgc tggcggagag gccgcctct 120
ccccggtatc agcgttccct cattctttga atccgcggct ccgcggtcct cggcgctcaga 180
ccagccggag gaagcctggt tgcaatttaa gcgggctgtg aacgcccagg gccggcgggg 240
gcggggccga ggcgggccat tttraataaa gaggcgtgcc ttccaggcag gctctataag 300
traccgccgc ggcgagcgtg cgcgckttgc aggtcactgt agcgggactt cttttggttt 360
tctttctctt tggggcacct ctggactcac tccccagcat gaaggcgtg agcccggtgc 420
gcggctgcta cgaggcgggt tgctgcctgt cggaacgcag tctggccatc gcccggggcc 480
gagggaaggg cccggcagct gaggagccgc tgagcttgct ggacgacatg aaccactgct 540
actcccgcct gcggraactg gtacccggag tcccagagg cactcagctt agccaggtgg 600
aaatcctaca gcgcgtcatc gactacattc tcgacctgca ngtagtcctg gccgagccag 660
ccctggacc cctgatggc cccaccttc ccatccagac agccgagctc gctccggaac 720
ttgtcatctc caacgacaaa aggagctttt gccactgact cggccgtgtc ctgacacctc 780
cagaacgcag gtgctggcgc ccgttctgcc tgggaccccg ggaacctctc ctgcccgaag 840
ccggacggca gggatgggcc ccaacttcgc cctgcccact tgacttcacc aaatcccttc 900
ctggagacta aacctggtgc tcaggagcga aggactgtga acttgtggcc tgaagagcca 960
gagctagctc tggccaccag ctgggcgacg tcacctgct cccacccac ccccaagttc 1020
taaggtctyt tcagagcgtg gaggtgtgga aggagtggct gctctccaaa ctatgccaaag 1080
gcggcggcag agctggtcct ctggtctcct tggagaaagg ttctgttgcc ctgatttatg 1140
aactctataa tagagtatat aggttttgta ccttttttac aggaagggtga ctttctgtaa 1200
caatgcgatg tatattaaac tttttataaa agttaacatt ttgcataata aacgattttt 1260
```

aaacaaaaaa aaaaaaaaaa aagggggggcc gccctanngg 1300

<210> 40  
<211> 215  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (210)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (213)  
<223> n equals a,t,g, or c

<400> 40  
cagaaacaga agttcacact aacagagtat ggttttaatt ttcctttgaa tgaaaaggat 60  
agaaagataa aattgtgtat tgtaacatg taaataaaat tggagctaata ttgaaactag 120  
cttctcaata acttcattctt tctagagact cattacctgt gggcttgctm aacctggact 180  
atttggccaa atwgggttga taaaaaaggn atntt 215

<210> 41  
<211> 474  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (85)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (216)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (374)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (449)  
<223> n equals a,t,g, or c

<400> 41  
tcgacccacg cgtccgggag actacggtaa aggcgcgcgc acgcagccaa catgccgggtg 60  
gcccgagact gggtttgcg caagnctacg tgaccctcgc gaggcccttt gagaagtcgc 120

```

ggctcgacca agagctgaag ctgataggcg agtacgggct ccggaacaaa cgtgagggtgt 180
ggaggggtcaa gttcaccctg gccaagatcc gcaagnccgc gcgggarctg ctgacgctgg 240
acgagaagga cccgcgggcgc ctgtttgagg gcaatgcctt gcttcggcga ctggtgcgca 300
ttggagtgtc ggacgagggc aagatgaagc tggattatat cctgggtctg aagatgagga 360
ttcttgaga grcntctgca gacccaggty tttcaagctg gggttggcca atccatccac 420
catgcctgt gctgatccgc caggccacnc aggtccgaaa gcaagtgggtg aaca 474

```

```

<210> 42
<211> 425
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (375)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (403)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (418)
<223> n equals a,t,g, or c

```

```

<400> 42
cctcgccttc gatgaatatg ggcgcctttt cctcatcatc aaggatcagg atcgcaagtc 60
tcgtcttatg ggactggagc tctcaagtct catatcatgg cggcaaaggc ttagcaaat 120
accatgagaa catcacttgg accaaatgga cttgataaaa tgatggtgga caaggacgac 180
gacgtgacgg tcacaaacga cggtgccacg attctgagca tgatggatgt cgatcaccag 240
attgccaaagc tgatggtgga gctgtccaaa tcccaggatg atgaaatcgg agatggggac 300
cacgggggtg gttgtcctgg ccggcgccct gctggaagga ggccgagcag ctgctggacc 360
gcggcattca mccgntcagg atcgccgacg gttacgagca ggntgcccgc attggccntc 420
gagca 425

```

```

<210> 43
<211> 1187
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (33)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (41)
<223> n equals a,t,g, or c

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<220>  
<221> misc feature  
<222> (1149)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1156)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1160)  
<223> n equals a,t,g, or c

<400> 43  
tgtgggaact ggtgggtccc ccgggctggc agnaattggg nacgcgggtc gcggttcttg 60  
tttgtggatc gctgtgatcg tcacttgaca atgcagatct tctggaagac tctgactggg 120  
aagaccatca ccctcgaggt tgagcccagt gacaccatcg agaattgtcaa ggcaaagatc 180  
caagataagg aaggcatccc tcctgaccag cagaggctga tctttgctgg aaaacagctg 240  
gaagatggkc gcaccctgtc tgactacaac atccagaaag agtccaccyt gcacctggtr 300  
ctccgtctca gaggtgggat gcaaatcttc gtgaagacac tcaactggcaa gaccatcacc 360  
cttgaggctg agcccagtga cacyatcgag aacgtcaaa caaagatcca rgacaaggaa 420  
ggcattcctc ctgaccagca gaggttgatc ttgcccggaa agcagctgga agatgggcgc 480  
accctgtctg actacaacat ccagaaagag tctaccctgc acctgggtgt cgtctcaga 540  
gggtgggatgc agatcttcgt gaagaccctg actggttaaga ccatcacycy cgargtggag 600  
ccgagtgaac ccattgagaa tgtcaaggca aagatccaag acaagggaagg catccctcct 660  
gaccagcaga ggttgatctt tgctgggaaa cagctggaag atggacgcac cctgtctgac 720  
tacaacatcc agaaagagtc caccctgcac ctggtgctcc gtcttagagg tgggatgcag 780  
atcttcgtga agaccctgac tggtaagacc atcactctcg aagtggagcc gagtgcacac 840  
attgagaatg tcaaggcaaa gatccaagac aaggaaggca tccctcctga ccagcagagg 900  
ttgatctttg ctgggaaaca gctggaagat ggacgcaccc tgtctgacta caacatccag 960  
aaagagtcca cctgcacct ggtgctccgt ctyagagggt ggatgcagat cttcgtgaag 1020  
accctgactg gtaagaccat cacyctcgaa gtggagccga gtgacacatc ygagaatgtc 1080  
aaggcaagat ccagacaagg aaggcatcct cctgaccagc agargttgat tttgctggga 1140  
aaarcttgna aatggncgan cccttttgat taaaatcccg aaagttc 1187

<210> 44  
<211> 515  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (217)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (465)

<223> n equals a,t,g, or c

<400> 44

```
ctgcagtacc gtccgaattc ccgggtcgac ccacgcgtcc ggtttgagcc gtcgtgcttc 60
accggtctac ctgcctagca tgtcgggccc cggcaagact ggcggcaagg cccgcgccaa 120
ggccaagtcg cgctcgtcgc gcgcggcct ccagttccca gtgggccgtg tacaccggct 180
gctgcggaag ggccactacg ccgagcgcgt tggcgcnggc rcgccagtgt acctggcggc 240
agtgtggag tacctcaccg ctgagatcct ggagctggcg ggcaatgcgg cccgcgacaa 300
caagaagacg cgaatcatcc cccgccacct gcagctggcc atccgcaacg acgaggagct 360
caacaagctg ctgggcggcg tgacgatcgc ccagggaagg cgttctgccc aacatccagg 420
ccgtgsttgy tgccaagaa gaccagcgcc accgtggggc cgaangccct tcggggggca 480
agaaagggca accaaggctt cccaaggagt actaa 515
```

<210> 45

<211> 1499

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1476)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1492)

<223> n equals a,t,g, or c

<400> 45

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gcgagtgcgc gtcctcctc gcccgccgct aggtccatcc cggcccagcc accatgtcca 60
tccacttcag ctccccgca tccgcgaggt caccattaac cagagcctgc tggccccgct 120
gcggtggag gccgaccct cctccagcg ggtgcgccag gaggagagcg agcagatcaa 180
gacctcaac aacaagtgtg cctccttcat cgacaaggtg cggtttctgg agcagcagaa 240
caagctgctg gagaccaagt ggacgctgct gcaggagcag aagtcggcca agagcagccg 300
cctcccagac atctttgagg ccagattgc tggccttcgg ggtcagcttg aggcactgca 360
ggtggatggg ggccgcctg aggcggagct gcggagcatg caggatgtgg tggaggactt 420
caagaataag tacgaagatg aaattaaccg ccgcacagct gctgagaatg agttgttgt 480
gctgaagaag gatgtggatg ctgcctacat gagcaaggtg gagctggagg ccaaggtgga 540
tgccctgaat gatgagatca acttccctcag gacctcaat gagacggagt tgacagagct 600
gcagtcccg atctccgaca catctgttgt gctgtccatg gacaacagtc gtcctctgga 660
cctggacggc atcatcgtg aggtcaaggc rcagtatgag gagatggcca aatgcagccg 720
ggctgaggct gaagcctggg accagaccaa gtttgagacc ctccaggccc aggctgggaa 780
gcatggggac gacctccgga ataccggaa tgagatttca gagatgaacc gggccatcca 840
gaggctcag gctgagatcg acaacatcaa gaaccagcgt gccaaagtgg aggccgcat 900
tgccgaggct gaggagcgtg gggagctggc gctcaaggat gctcgtgcca agcaggagga 960
gctggaagcc gccctgcagc gggccaagca ggatatggca cggcagctgc gtgagtacca 1020
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ggagggcgag gagagccggt tggctggaga tggagtggga gccgtgaata tctctgtgat 1140
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gggcagcaat gccctgagct tctccagcag tgcgggtcct gggctcctga aggcttattc 1260
catccggacc gcatccgcca gtcgcaggag tgcccgcgac tgagccgcct cccaccactc 1320
```

cactcctcca gccaccaccc acaatcaciaa gaagattccc acccctgcct cccatgcctg 1380  
gtcccaagac agtgagacag tctggaaagt gatgtcagaa tagcttccaa taaagcagcs 1440  
tcattctgag gcctgagtga aaaaaaaaaa aaaaanaaaa aaaaaaattt tngggggggg 1499

<210> 46

<211> 393

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (167)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (178)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (219)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (359)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (372)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (378)

<223> n equals a,t,g, or c

<400> 46

tcgacccacg cgtccggcag cctttctgag ggagcgggtg tgtgttcgcc atcttaggaa 60  
gaagatgttc tcgtccgtgg cgcattctggc cgggcgaacc ccttcaacgc gccccacctg 120  
cagctggtac acgatggcct cacgggcacc gaagcagccc cgtgggnacc cccgggcneg 180  
ccccgaacgt tcccgaatc tggcagcagc cgctgtggna agagtacagt tgcgaatatg 240  
gtcccatgaa gttttatgca ctgtgtggct ttggtggggt ctttaagttgt ggtctgacac 300  
acactgctgt cgttcctctg gatttagtga aatgccgaat gcargtggac cccagaant 360  
acaagggcak wnttaatngg attctcatta aca 393

<210> 47

<211> 238

<212> DNA



<213> Homo sapiens

<400> 47

```
cggatccccg ctcctgcac cagtcgccat tcgggaggcc gctgcgctgc agggcctcgc 60
ggaccgcccg cgaccgcgag ccgggccctc cgcgcggtcc atcgcccact ggacgccgcc 120
cgcggccgga ccggttcaac ttctcatctt tggtcttctt catatactat aggctgtttg 180
ctgtggttta gtcaaaaagc catgtagaat gcctgccttt tgaagaccac ttttaagg 238
```

<210> 48

<211> 939

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (937)

<223> n equals a,t,g, or c

<400> 48

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gccaccatct tggaacggga ggcgagcag agtcgactgg gagcgaccga gcgggccgcc 60
gccgcgccca tgaacccccga atatgactac ctgtttaagc tgcttttgat tggcgactca 120
ggcggtggga agtcatgcct gctcctgcgg ttgtctgatg acacgtacac agagagctac 180
atcagcacca tcggggtgga cttcaagatc cgaaccatcg agctggatgg caaaactatc 240
aaacttcaga tctgggacac agcgggccag gaacggttcc ggaccatcac ttccagctac 300
taccgggggg ctcatggcat catcgtggtg tatgacgtca ctgaccagga atcctacgcc 360
aacgtgaagc agtggctgca ggagattgac cgctatgcc a gcgagaacgt caataagctc 420
ctgggtggga acaagagcga cctcaccacc aagaagggtg tggacaacac cacagccaag 480
gagtttgag actctctggg catcccttc ttggagacga gcgccaagaa tgccaccaat 540
gtcagagcag cgttcatgac catggctgct gaaatcaaaa agcggatggg gcctggagca 600
gcctctgggg gcgagcggcc caatctcaag atcgacagca cccctgtaaa gccggtggc 660
ggtggctgtt gctagsaggg gcacatggag tgggacagga gggggcacct tctccagatg 720
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<210> 49

<211> 1771

<212> DNA

<213> Homo sapiens

<400> 49

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tgaccaaaag tagccagtt ttctgagttc ccgtgtgcta gactggccag aagagagggt 480
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```

```

tccagtctgg ttttgagagc aggggctggt ctgcagcacc kcagggaagg gaggagagat 600
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caaaggtcag tgacagtttc tcagaagagg cccagcgtcc acctctctcc cagggccaga 1620
cacccttcc tggctcccc atccccctat ggctcccagc cccttgacc ctcattgctg 1680
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aaaaaaaaa aaaaaaaaaa aaaaaattt t 1771

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<210> 50

<211> 397

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (201)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (207)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (352)

<223> n equals a,t,g, or c

<400> 50

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gggtcgaccc acgcgtccgc tcgtccggg atcgcccgcg ctagagacgc atagcgtct 60
aatcgtcgc acgcaccggc cctcgtcgc tcgccgtcc gtgcccgcgc cgccagccc 120
accgccaccc tttgcagcca tgcaccag gtcygtgtcc tcgtcytct accgcagatg 180
ttcgcgggcc ccggcaccgg naggcgnccg agctccacgc gcataacgtg accagtccac 240
ccgcacctac agcctgggca gcgcctgcgc cccagcacca gccgcagcct ctamamctcg 300
tccccgggcg gcgcgtatgt tcacggctcc ttccgcggtg cgcctgcgga anatgttgcc 360
ccggcggtgc gcttgctggc aggattccgt ggaattt 397

```

<210> 51  
<211> 1635  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1422)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1617)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1620)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1629)  
<223> n equals a,t,g, or c

<400> 51  
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ccatcaaggc ctcctccggc ctggggggcg gctcgtcccg cacctcctgc cggtgtctg 180  
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agtactacag gacaattgag gagctgcaga acaagatcct cacagccacc gtggacaatg 540  
ccaacatcct gctacagatt gacaatgccc gtctggctgc tgatgacttc cgcaccaagt 600  
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tgggtggtga gatcaatgtg gagatggacg ctgccccagg cgtggacctg agccgcctcc 840  
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tgccagagtg caagagttag atctcggagc tccggcgcac catgcaggcc ttggagatag 1020  
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gaggactcag ctaccccggc cggccacca ggaggcagg angcagccgc ccatctgcc 1440  
ccacagtctc cggcctctcc agcctcagcc ccctgcttca gtcccttccc catgcttctc 1500

tgctgatga caataaagct tgttgactca gctaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560  
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanttn 1620  
ggggggggnc ccccc 1635

<210> 52

<211> 1780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1780)

<223> n equals a,t,g, or c

<400> 52

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ggggtgatcc tgctggctgt tggagtctgg ggcaaaactta ctctgggcac ctatatctcc 180  
cttattgccg agaactccac aaatgctccc tatgtgctca tcggaactgg caccactatt 240  
gttgtctttg gcctgtttgg atgctttgct acatgtcgtg gtagcccatg gatgctgaaa 300  
ctgtatgcca tgtttctgtc cctggtgttc ctggctgagc tcgtagctgg catttcaggg 360  
tttgtgtttc gtcattgagat caaggacacc ttcttgagga cttacacgga cgctatgcag 420  
acttacaatg gcaatgatga gaggagccgc gcagtggacc atgtgcagcg casctgagct 480  
gctgtggtgt gcagaactac accaactgga gcaccagccc ctacttctctg gagcatggca 540  
tccccccag ctgctgcatg aacgaaactg attgtaatcc ccaggatcta cacaatctga 600  
ctgtggccgc caccaaagtt aaccagaagg gttgttatga tctggtaact agtttcattg 660  
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gcatgtgctt ggccctgtgt ctgtcccggt tcatcacggc caatcagtat gagatggtgt 780  
aaggagaagt ctttcaagaa tgacggaata agagacctgt tttaaaaagg aactgcagca 840  
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aatttaaaaa tgagtgtgaa gggggaacaa gtcaaaatat ttttaaaaga tcttcaaaaa 1680  
taatgcctct gtctagcatg ccaacaagaa tgcattgata ttgtgaacat ttgtgatata 1740  
tgtattaata aatagagcaa ttacaagcaa aaaaaaatgn 1780

<210> 53

<211> 490

<212> DNA

<213> Homo sapiens

&lt;400&gt; 53

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gggggggtgg ggatccagct tattctttta ttttcaagtc cattcttggg gctgggtggg 120  
aggcaggaga ataccctcc ctaagccctt agtgtgtgcc gagcttgctt tgtgatgttg 180  
gcaggggagg ggagacctgg gtggtgactg agttcccttt atcaaaccct tcaatgggca 240  
caaaattgag tgcttgattt taggttttat ttttttatga atgtccaaat ctgtgtttcc 300  
ccctgccctc ccagactgtg tggccagtgt aaagtgtctg gtttgtgttc atctctccct 360  
catttctgga gcagggcctg agaccctgcc acatctccta tgctctgcat ccacgcctct 420  
tttgacatt aaaggttgat tgatgcaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480  
aaaaaaaaaa 490

&lt;210&gt; 54

&lt;211&gt; 1944

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (466)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (634)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1308)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 54

acggtacgga attcccgggt cgaccacgc gtccgacccc ggaccggag tcgcgagag 60  
ctgggcagtg ttggccgctg gcggagcgtc ggggcagcat gaagtgcctg gtcacgggcg 120  
gcaacgtgaa ggtgctcggc aaggccgtcc actccctgtc ccgcatcggg gacgagctct 180  
acctggaacc cttggaggac gggtctctcc tccggacggt gaactcctcc cgctctgcct 240  
atgcctgctt tctctttgcc ccgctcttct tccagcaata ccaggcagcc acccctgggc 300  
aggacctgct gcgctgtaag atcctgatga agtctttcct gtctgtcttc cgctcactgg 360  
cgatgctgga gaagacggtg gaaaaatgct gcctctccct gaatggccgg arcagccgcc 420  
tggtggtcca gctgcattgc aagttcgggg tgcggaagat camaanctgt ccttcmagga 480  
ctgtgagtcc ctgcaggccg tcttcgaccc agcctcgtgc cccacatgc tccgcgcccc 540  
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gggcattggc cgtggcgagc gktcctcctg gcantaccac gaggaggagg cagacagcac 660  
tgccaaaagcc atggtgactg agatgtgcct tggagaggag gatttccagc agctgcaggc 720  
ccaggaaaggg gtggccatca ctttctgcct caaggaatc cgggggctcc tgagctttgc 780  
agagtcagca aacttgaatc ttatgcattca ttttgatgct ccaggcaggc ccgcatctt 840  
caccatcaag gactctttgc tggacggcca ctttgtcttg gccacactct cagacaccga 900  
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catggaacc actataggca atgagggtc gcgggtgctg ccctccattt ccctttcacc 1080  
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tgccctggct ggggcccggg gccgagactc ccaagcggst ctgtgcagaa gagctgccag 1860
gcagtgtctt agatgtraga cggaggccat ggcgagaatc cagctttgac ctttattcaa 1920
gagaccagat gggtttgccc cagg
1944

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<210> 55

<211> 994

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (896)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (971)

<223> n equals a,t,g, or c

<400> 55

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cgcgagagcg ktatctgcgt gtccggacgt gcggaggctc tcactttccg tcatggcgct 120
gaaggtagcg accgtcgccg gcagcgccgc gaaggcgtgc tcgggccagc ccttctctgc 180
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acaattcctc cgtccgctaa gtatggcggg cggcacacgg tgaccatgat cccaggggat 300
ggcatcgggc cagagctcat gctgcatgtc aagtccgtct tcaggcacgc atgtgtacca 360
gtggactttg aagaggtgca cgtgagttcc aatgctgatg aagaggacat tcgcaatgcc 420
atcatggcca tccgcgggaa ccgcgtggcc ctgaagggca acatcgaaac caaccataac 480
ctgccaccgt cgcacaaatc tcgaacaac atccttcgca ccagcctgga cctctatgcc 540
aacgtcatcc actgtaagag ccttcaggc gtggtgaccc ggcacaagga catagacatc 600
ctcattgtcc gggagaacac agagggcgag tacagcagcc tggagcatga gagtgtggcg 660
ggagtgttg agagcctgaa gatcatcacc aaggccaagt ccctgcgcat tgccgagtat 720
gccttcaagc tggcgagga gagcgggcgc aagaaagtga cggccgtgca caaggccaac 780
atcatgaaac tgggcgatgg gcttttctc cagtgtgca gggaggtggc agcccgctac 840
cctcagwtca ccttcgagaa catgattgtg gataacacca ccatgcagct ggtgtncgg 900
ccccagcagt ttgatgtcat ggtgatgcc aatctctatg gcaacatcgt caaacaatgt 960
ctgcgcggga ntggtcgggg gcccaagctt gttg
994

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<210> 56

<211> 328

<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (123)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (156)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (170)  
<223> n equals a,t,g, or c

<400> 56  
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gtagccttg ccctttttca tctgagtccc atttagagat gtataaagaa tgttggtgag 120  
tanggcgcgg tggtcacgc ctgtaatccc cacacnttgg gaaggccgan gcaggcggat 180  
cacgaggtca gaagattgag accattctgg ctaacatggt gaacccccat ctctactaaa 240  
aatacaaaaa ttagtcaggc gcgatggcgg gcacatgtag taccagctac tcgggaggct 300  
gatgcagaag aataacttgg aacctggg 328

<210> 57  
<211> 1489  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (710)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1109)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1117)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1206)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1211)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1218)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1264)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1311)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1446)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1467)  
<223> n equals a,t,g, or c

<400> 57  
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gctgaagggc ctcgagttcc ttccagagac tgtatttgac acactttagg tacacacaaa 120  
cgaatggtat cacatgcaat attttaattg agcaatggga gaggctcttt gaaatggggt 180  
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tgtttgagca tgcaggggcc atggggagtt tgggtgctagt tgggtggagaa gggactagat 360  
ggcatctctt agccgaggcc aacaggaact gcacaagtcc attatagtca aagtttagca 420  
ttttgatacg taaacacaat acttcattct tcctcatctg agctttcctt ccttcttctt 480  
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gtgtctgaac ccagttcagt ttatctccag ttgaaacgat atacactata ttatgtataa 840  
atgtatacac acttcctata tgtatccaca tatatatagt gtatatatta tacatgtata 900  
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tccagatgct cattacaaa ccagatgcta cacaacagc agcagaggaa acaagggttg 1020  
actcttgcaa cagatcacia aaaataaaaa cagctacttg cagtgaactt ggtcatttct 1080  
gtatgttcat aaagaatgga ttgtaacna ggaaaanaag gaccagtgtt agtgaaaagg 1140  
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```

cagtantcat ntagtcangt gattgattca gttctgctat gaaacattgt aacacgtacc 1260
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<210> 58
<211> 1283
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (38)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (550)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (1242)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (1250)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1260)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (1263)
<223> n equals a,t,g, or c

```

```

<400> 58
aggtaatttg aattgagaga gagtaagtga cttgctgnaa aaaggggttaa tcaacagcag 60
agctgggatt tgaaccata actctgtcaa agcctccact cctaactcct gttcatgctc 120
ctgtggagaa aatgcttgta gtaacatatt ttaaattgtac taacaagacc agtcatgggm 180
aaatgtttct gagacaaatc tctagtttat gatttaaaac agtacgtttt cttacgtgac 240
gaaaacaaaa agtgtgttaa tttgttccca gtggttgaag ttatttgcca acaattttac 300
tgttttctct catctgttta taggatttct ctgcctcttc caaacttttc ctccctgaac 360
ctgaggggta agcattttat ttccctttag gaaaaacgct agctgcttgt aaccactgtg 420
tttatgtcaa agcattcatt ttttttagga tatctgaaaa aatgccatat aagaaaaaam 480
tctataaaac atctatwatt ttcgaacca agtacactct tgcattctaw gctttaagtt 540

```

```

aaatgcaaan tcctttttcc ttcttctctgc tgcaagtact atctcatcct gatgctcaag 600
agtgtcaggg cctgggtttc caaacagaga ctaccctaaa attatttggc gagtagtact 660
ttacacaatt gcctctcccc cacaaatcat aattgtttca gtaaaatggg tacttggttt 720
ttccaagaaa aaactcgttt ttactcattt ttggcctgtt tgtttattta gaaactaatc 780
tggtttcact ccctctgggt gataccctact caaaaaggac acttctgatt aagacgggtg 840
aaactagaga tggacaggtt atcaacgaaa cttctcagca tcacgatgac cttgaataaa 900
aattgcacac actcagtgcg gcaatatatt accagcaaga ataaaaaaga aatccatata 960
ttaaagaaac agctttcaag tgcttttctg cagtttttca ggagcgcaag atagatttgg 1020
aataggaata agctctagtt cttacaacc gacactccta caagatttag aaaaaagttt 1080
acaacataat ctagtattaca gaaaaatctt gtgctagaat acttttttaa aggtattttg 1140
aataccattt aaactgcttt tttttttcca gcaagtatcc aaccaacttg gttctgcttc 1200
aataaatctt tggaaaaact maaaaaaaaa aaaaaaaaaam mngggggggg gcccggggtt 1260
ccnccggggg gcccaagttt tac 1283

```

&lt;210&gt; 59

&lt;211&gt; 740

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (696)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 59

```

agaaggagcg cggggaggac gtacctgtgt agatgcgagc cggccaacag cttgcaagca 60
tgctccgctg gacccgagcc tggaggctcc cgcgtgaggg actcggcccc cacggcccta 120
gcttcgagag ggtgcctgtc gcacccagca gcagcagcgg cggccgaggg ggcgcccagc 180
cgaggccgct tccgctttcc tacaggcttc tggacgggga ggcagccctc ccggccgctc 240
tctttttgca cgggctcttc ggcagcaaaa ctaactcaa ctccatcgcc aagatcttgg 300
cccagcagac aggccgtagg tgctgacggt ggatgctcgt aaccacggtg acagccccc 360
cagcccagac atgagctacg agatcatgag ccaggacctg caggaccttc tgcccagct 420
gggctcgtgt ccctgcgtcg tcgttggtcca cagcatggga ggaagacag ccatgctgct 480
ggcactacag aggccagagc tgggtggaac tctcattgct gtagatatca gccagtgga 540
aagcacaggt gtctccact ttgcaacctt tgtggcagcc atgagggcca tcaacatcgc 600
agataggctt gccccgctcc cgtgccgaa aactggcgga tgaacagctc agttctgtca 660
tccaggacat ggccgtgcgg cacacttgct tcaatnaacc tggtagaggt agacgggct 720
tttcgtgttg gaggtggaa 740

```

&lt;210&gt; 60

&lt;211&gt; 1291

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (6)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

<222> (7)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (147)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1211)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1283)  
<223> n equals a,t,g, or c

<400> 60  
actttnnccc ctcccccttt cctttcccggt ctcacgcgcc aggccgcttg cacatgcgca 60  
ttaaggtacaa agcctcgctc tttgtcccca tctgtcggtc acacgaactc aagcctttgg 120  
cattcggcag ccaatagaat ctaaganatg gcggaataat gattccgcct cgggagctaa 180  
acttgattgg cagtttagct aaccaatcga gaacgccatt tgtamccctt ggcaggcamc 240  
gagctccgct gtctcggttc cggcggtcgc gcgctctttt ctcgggacgg gagaggccgt 300  
gtagcgtcgc cgttactccg aggagatacc agtcggtaga ggagaagtcg aggttagagg 360  
gaactgggag gcactttgct gtctgcaatc gaagttgagg gtgcaaaaat gcagagtaat 420  
aaaactttta acttgagaa gcaaaacat actccaagaa agcatcatca acatcaccac 480  
cagcagcagc accaccagca gcaacagcag cagccgccac caccgccaat acctgcaaat 540  
gggcaacagg ccagcagcca aaatgaaggc ttgactattg acctgaagaa ttttagaaaa 600  
ccaggagaga agaccttcac ccaacgaagc cgtctttttg tgggaaatct tcctcccgac 660  
atcactgagg aagaaatgag gaaactattt gagaaatatg gaaaggcagg cgaagtcttc 720  
attcataagg ataaaggatt tggctttatc cgcttggaac cccgaaccct agcggagatt 780  
gccaaagtgg agctggacaa tatgccactc cgtggaaagc agctgcgtgt gcgctttgcc 840  
tgccatagt catcccttac agtcgaaac cttcctcagt atgtgtccaa cgaactgctg 900  
gaagaagcct tttctgtgtt tggccaggta gagagggtg tagtcattgt ggatgatcga 960  
ggaaggccct caggaaaagg cattgttgag ttctcaggga agccagctgc tcggaaagct 1020  
ctggacagat gcagtgaagg ctcccttcctg ctaaccacat ttcctcgtcc tgtgactgtg 1080  
gagcccatgg accagttaga tgatgaagag ggacttcag agaagctggg tataaaaaac 1140  
cagcaatttc acaaggaacg agagcagcca cccagatttg cacagcctgg ctcccttkga 1200  
gtatgaatat ngccatgcgc tgggaaggca ctcatgaga tggagaaagc agcctggggg 1260  
gacaagaagt gaagactcct gnttccaaaa a 1291

<210> 61  
<211> 971  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (856)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (886)  
<223> n equals a,t,g, or c

<400> 61  
ctgcagtacc ggtccggaat tcccgggtcg acccaacgcgt ccgggtctgt ggtcctctct 60  
cggtcctctcg cggtcgcgg cgcccgacgg ttcttgggac acctgcttgc ttggcccgtc 120  
cgccgggtca gggcttctct gctgcgtcc cggttcgctg gacgggaaga agggctgggc 180  
cgtcccgctcc cgtcccatc ggaacccaa gtcgcgcgc tgaccgctcg cagggcgaga 240  
tgagcgcgga cgagcggcc ggggcgccc tgcccggtct ctgctgctg gagaagggtc 300  
cgaacggcta cggttccac ctgcacggg agaagggcaa gttgggcccag tacatccggc 360  
tggtggagcc cggtcgcgg gccgagaagg cggggtgct ggcgggggac cggctggtgg 420  
aggtgaacgg cgaaacgtg gagaaggaga cccaccagca ggtggtgagc cgcattccgcg 480  
ccgcactcaa cgccgtgcgc ctgctggtgg tcgacccga gacggacgag cagctgcaga 540  
agctcggcgt ccaggtccga gaggagctgc tgcgcgcca ggaagcgcg ggcaggccg 600  
agccgcggc cgccgcrag gtgcagggg ctggcaacga aaatrarcct cgcraggccg 660  
acaagagcca cccggagcag cgcgagcttc ggcctcggt ctgtaccatg aagaagggcc 720  
ccagtggcta tggcttcaac ctgcacagcg acaagtccaa gccaggcccag ttcattccgt 780  
cagtggaacc agactcccc gctgaggtt cagggtccg ggcccaggat cgcattgtgg 840  
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caccttgggg cagccatcat accatcatgg ggtttgatta gccacgggc attagccaac 960  
ctgggaggtt g 971

<210> 62  
<211> 618  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (563)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (598)  
<223> n equals a,t,g, or c

<400> 62  
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ggaccacgc tgcattttca tcgaaagagt gaacatctag tgggactgaa agttctttgt 120  
tgtttcagat tgtagagtgt gattgatgga attggtctgt ggaaattgca ttgtttttat 180  
ttctttatgt aatcagttta agtaatagg ggtatatata atcgtaagta ttttaggggtg 240  
ggaggggcta ttaagtaatt aagtgggtgg ggttagttta aaagttagca tgatatgtat 300  
tagataactc tataagtgga catgtgtact tacttgat cctttaccct atgattgcta 360  
cccttaacga tttcaataa actcagagg aactgcagg agatcaaacc atttagggca 420  
aattggacat gaataaaact ctagtgggaa aaagttcaaa ggtgattgaa taaataattt 480  
aactttgccc tgggtattaa gtccagggt cccagattgt ggagcagagc cttggagagt 540  
acaggatgaa ggagatagat gcnccttga ctgcccggga atgaaattgg attaatgnaa 600

ggatggtaaa taattcca

618

&lt;210&gt; 63

&lt;211&gt; 1138

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (7)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (15)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (22)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (27)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (29)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1123)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 63

tctatanatc atganaggaa anggtancng acagtacggt cggattcccg ggtcgacceca 60  
cgctccgatg acttcacccc tctggagatc ctctggacct tctccatcta cctggagtca 120  
gtggccatct tgccgcagct gttcatggtg agcaagaccg gcgaggcgga gaccatcacc 180  
agccactact tgtttgcgct aggcgtttac cgcacgctct atctcttcaa ctggatctgg 240  
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gtcctctact gcgatttctt ctacctctat atcaccaaag tcctaaaggg gaagaagttg 360  
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ggaaggcggc agaagatgaa gagctttccc atccagggtg gactttttta agaaccacc 480  
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ttggggagct caggacttgg gctgtttgta gttttttgcc ttttagacaa gaaaaaaaaa 600  
tctttccact ctttagtttt tgattctgat gactcgtttt tcttctactc tgtggcccca 660  
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ttttcatagt aattttttcc cccagagttt gaattttttg gtcttctcct ggttttttgg 960  
caaattaggg gggcccgagg ctcaagtgcg ggaagggggc tggcccgagg atcccatggc 1020  
tctcacacca tgtttttgta cagaactgat ggttgaatct ttgttctctt gaaataaaca 1080  
gaagaaaatg aaaccttaaa aaaaaaaaaa aaaaaaaaaa acncggggggg gggcccg 1138

<210> 64

<211> 418

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (365)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (371)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (380)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (391)

<223> n equals a,t,g, or c

<400> 64

tgctcatcca gaggagctca ccacagtcac tgcgacagac tgccacactc accctggcct 60  
ggcctcagag aagttgagct actggcctca gttcacacag agcagatgga ggaagagctg 120  
gcactaggac ccagggggca ggggggagcc tccctggctg gaagggatgg caggagcgct 180  
ggtgcaggta gctatggagc tctggccaac tctgcctggg gaggtcccag gaaggtggcg 240  
tcagcatctg cagccgcgtc gacgttgctg gagcctccgc ggaggaccca ggagagccgg 300  
actaggacca gggccctggg cctccccaca ctcccatgg agaagctggc ggccctctaac 360  
agagncccaa ngggcttggg cggtcctggg ncgtgaaaat gttcaagtgc ccgattga 418

<210> 65

<211> 2836

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2834)

<223> n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2836)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 65

```
aagaaaccgc ccattacaca cccagtagca ccagcagagg aaacttataa cctcgggagg 60
caggtccttc ccctcagtag ggtcacatac ttccagaaga gcggaccagg gctgctgcca 120
gcacctgcca cttagagcgc ctctgtcgtc gggacccttc agaactctct ttgctcaca 180
gttacaaaaa aaaaagagc caacatgttg gtattgctgg ctggtatctt tgtggtccac 240
atcgctactg ttattatgct atttgtagc accattgcca atgtctggtt ggtttccaat 300
acggtagatg catcagtagg tctttgaaa aactgtacca acattagctg cagtgcagc 360
ctgtcatatg ccagtgaaga tgccctcaag acagtgcagg ccttcagatg tctctctatc 420
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aaccggttct tcctctcagg gggscaccaca ctggtgtgct gscctgtgcat tctgtgagg 540
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cctacatcct gggctggatc tgcttctgct tcagcttcat catcggcggt ctctatctgg 660
tcctgagaaa gaaataaggc cggacgagtt catggggatc tgggggggtg ggaggaggaa 720
gccgttgaat ctgggaggga agtgagggtt gctgtacagg aaaaaccgag ataggggagg 780
ggggaggggg aagcaaaggg gggagggtcaa atcccaaacc attactgagg ggattctcta 840
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ggaatactca cattttgtaa agaagttgaa ctatgactgg agtaaaccat gtattccctt 2580
atcttttact tttttctgtg gacatttatg tctcatgtaa tttgcattac tctggtggat 2640
tgttctagta ctgtattggg cttcttcggt aatagattat ttcatactat ataattgtaa 2700
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atattttgat acaaagtgtt ataactctag ggatataaaa acagattctg attcccttca 2760  
ttgtgtgaat gtttttttct aaaaaaatg tggagaaata tggataatta tgacatttat 2820  
ccctcattaa agcngn 2836

<210> 66

<211> 2305

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1973)

<223> n equals a,t,g, or c

<400> 66

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cgcgctcatc tgctggagcc cgagcgsaa cagcttccac gtgttcgacc agggccagtt 120  
tgccaaggag gtgtgcccc agtacttcaa gcacaacaac atggccagct tcgtgcggca 180  
gytcaacatg tatggcttcc ggaaagtggc ccacatcgag cagggcgkcc tggcaagcc 240  
agagagagac gacacggagt tccagcacc atgcttccctg cgtggccagg agcagctcct 300  
tgagaacatc aagaggaaag tgaccagtgt gtccaccctg aagagtgaag acataaagat 360  
ccgccaggac agcgtcacca agctgctgac ggacgtgcag ctgatgaagg ggaagcagga 420  
gtgcatggac tccaagctcc tggccatgaa gcatagagaat gaggtctctgt ggcgggaggt 480  
ggccagcctt cggcagaagc atgcccagca acagaaagtc gtcaacaagc tcattcagtt 540  
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gctgaacgac agtggctcag cacattccat gcccaagtat agccggcagt tctccctgga 660  
gcacgtccac ggctcgggccc cctactcggc cccctcccca gcctacagca gctccagcct 720  
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gccctgctgg acctgttcag cccctcgtg accgtgcccg acatgagcct gcctgacctt 1260  
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ccacagagat acacagatat atacacagag tggatggacg gacaagacag gcagagatct 1920  
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cctgggggaa gacggatgtt gcagctagct ccgtgcctgc ccgactcccc aggaccagca 2100  
tgtgcttgca gttctttatt gagggaccag ggggtgggagc ctcaccttg cctggggggt 2160



ctctggttgt cacaggacca ccaggaaccc ccttcccaag gtgttcgcac tcggacaggt 2220  
gatgcggggc gggcacactg tctttctgcc agagccagca ccctgtgtag gcacggggaa 2280  
cgggagcctg tcccgtagct ttagg 2305

<210> 67  
<211> 1907  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1221)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1655)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1896)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1904)  
<223> n equals a,t,g, or c

<400> 67  
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tcagcctgaa aatccctgaa attagcatcc aggatatgac agcccagggt accagcccat 120  
cgggcaagac ccatgaggcc gagatcgtgg aaggggagaa ccacacctac tgcattccgt 180  
ttgttcccgc tgagatgggc acacacacag tcagcgtgaa gtacaagggc cagcacgtgc 240  
ctgggagccc ctccagttc accgtggggc ccctagggga agggggagcc cacaagggtcc 300  
gagctggggg ccctggcctg gagagagctg aagctggagt gccagccgaa ttcagtatct 360  
ggaccgggga agctggtgct ggaggcctgg ccattgctgt cgaggggccc agcaaggctg 420  
agatctcttt tgaggaccgc aaggacggct cctgtggtgt ggcttatgtg gtccaggagc 480  
caggtgacta cgaagtctca gtcaagttca acgaggaaca cattcccgc agccccttcg 540  
tggtgcctgt ggcttctccg tctggcgacg cccgcccct cactgtttct agccttcagg 600  
agtcagggt aaaggtcaac cagccagcct cttttgcagt cagcctgaac ggggccaagg 660  
gggcgatcga tgccaagggt cacagcccct caggagccct ggaggagtgc tatgtcacag 720  
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gtgtcacagg gaaccagct gagttcgtc tgaacacgag caatgcggga gctggtgccc 960  
tgtcggtgac cattgacggc ccctccaagg tgaagatgga ttgccaggag tgccctgagg 1020  
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gcggccccta ccacattggg ggcagcccct tcaaggccaa agtcacaggc cccgtctctg 1140  
tcagcaacca cagcctccac gagacatcat cagtgtttgt agactctctg accaaggcca 1200  
cctgtgcccc ccagcatggg nccccgggtc ctgggcctgc tgacgccagc aaggtggtgg 1260

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ggagatcctg gtgaagcacg tgggcagccg gctctacagc gtgtcctacc tgctcaagga 1440
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gcctgtcact gcagccgccc ctgccctgtg ccgtncctgc ctcacctgcc tccccagcca 1680
gccgtgacc tctcggttt cacttgggca gaggagacca tttggtggcg ctgcttgct 1740
tctttggttc tgggaggggt gagggatggg ggtcctgtac acaaccacc actagtctc 1800
ttctccagcc aagaggaata aagttttgct tccattcwma aaaaaaaaaa aaaaaaaaaa 1860
tygggggggg kccgktaacc caattggcct ttaagngggg ggtntta 1907
```

&lt;210&gt; 68

&lt;211&gt; 815

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 68

```
gggtcgaccc acgcgtccgt tttttttaag tgtgaatttt ttattgagat aaacaacagc 60
ataaagaata caagtagcca aatggttttg aaaaaccaa ttaggtcaaa gttctaaatt 120
aaaaatagca gttgtgtttc aatttacctt attctagcaa ttwaagtwgg taacatacaa 180
atagttatwc tgatacaaga tattaaagac atactcagtt ttaatcaact acctctcaag 240
aaacagtagg gcctctgtaa aattggagac tgataggttg atcagaaact caccctaaat 300
ctgaacgggt gccgctataa tttgtgacat ctggcaagat ttccctttat gtatatattt 360
taacaatccg cttggacacg aacaaagcca cacttctaac tgcttctggc gaactgattt 420
tatttttaat ttttttcaat aaagatatc ttagatactg aaagaaatag ttaatgagtt 480
tgcatgtgtg cttgagaaaaa tttggctcaa gtccatttg ctgtagtgtc aacgatgttt 540
ccagtagtgt ttagatttgg tgtcttcaaa ggtagtgtat taaaaccaag tgtgtcttta 600
atatcttgta tcagaataac tttgtatgtt accaacttaa attgctagaa taaggtaaatt 660
tgatacacia ctgctatttt taatttagaa ctttgacctt atttgggttt tcaaaacct 720
tttggtact tgtattcttt atgctgttgt ttatttcaat aaaaaattca cacctaaatg 780
tatacttact aaaaaaaaaa aaaaaaaaaa actcg 815
```

&lt;210&gt; 69

&lt;211&gt; 1150

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (14)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (20)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (25)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1150)

<223> n equals a,t,g, or c

<400> 69

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tggggtgcc cttggagctg tgccaaagct acacctcggg gtcctagtct caactggcct 180
gcgtactgct gtgggctcac ccgccttcc tcccacagcc ctgggcgctg cctatggcac 240
agccaagagc ggtaccggca ttgcggccat gtctgtcatg cggccggagc agatcatgaa 300
gtccatcatc ccagtggcca ttgctggcat catcgccatc tacggcctgg tggaggcagt 360
cctcatcgcc aactccctga atgacgacat cagcctctac aagagcttcc tccagctggg 420
cgccggcctg agcgtgggcc tgagcggcct ggcagccggc tttgccatcg gcatcgtggg 480
ggacgctggc gtgcggggca ccgccagca gcccgcacta ttcgtgggca tgatcctgat 540
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aaagtagacc ctctccgagc ccaccagcca cagaatatta tgtaaagacc acccctcctc 660
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cgtgccgtgg acatctgggc ccaactcatg cccctccagg ccccggcgc cccacccctc 840
agagtgtctt gtgtatgcgg atgatttaga attgtcattt ctctttactg gatgtttatt 900
tataaagatc tggcctgttc ctgcgtctgc ggagcggccc ttgtctccca gctatctata 960
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cctcaccgcc gggcccgtgg ccctgcgcgg agctgtgtcc aataaagttc ttggatgtga 1080
aaaaaaaaa aaaaaaaaaa aaaaaaaraa aaaaaaaaaa aaaraaaraa aaaaaawaa 1140
gaaaaaaaaa 1150
```

<210> 70

<211> 344

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (287)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (333)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (339)

<223> n equals a,t,g, or c

<400> 70

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caaagtctat tctccagttg ccagagtcag agctgggtga atactctctg gggggctaca 180
gtatttcatt tctgaaacag ctcatgtctg gcaaaactcca ggagtcgggt ccagaccctg 240
agctgattga tctgatatac tgtggccgga agcttaaaga tgaccanacc ttgacttcta 300
cgtattcaa cctggctcca catccatgtt ctncggaant cctg 344
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<210> 71

<211> 448

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (425)

<223> n equals a,t,g, or c

<400> 71

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tcgaccacag catccgaaga tgttcttgct gccccttccg gctgccgggc gagtcgtcct 60
ccgacgtctg ggcgtgaaca gttctgggca cgggtctcgc ccgccgcaga catgacgaag 120
ggtcttggtt taggaatcta tagtaaagac aaagaagatg atgtgccaca gtttacgagt 180
gcaggagaga atttcgataa attgggtgtct ggaaagtga gagaaatctt gaacatatct 240
ggacctcctc tgaaagcagg caaaaccgga accttttatg gtctgcatga ggacttcccc 300
agcgtggtgg tggtcggcct cggcagaaaag gcagctggag tcgatgacca ggaaaactgg 360
cmtgaaggca aagaaaacat cagagtcgcc atgcaacggg gtgcaggcag gttccaagac 420
ctggnaatct ctctctgtga aggtggat 448
```

<210> 72

<211> 2825

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2093)

<223> n equals a,t,g, or c

<400> 72

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gagaaggagg tcgcgcggcc tcacccggg ccgcgccccca ggccgcgcgc ggccccgcgc 60
tcatgaggtt gctcgcgcgc ccccgccgat cgccatggat cggatgaaga agatcaaacy 120
gcagctgtca atgacactcc gaggtggccg aggcatagac aagaccaatg gtgcccctga 180
gcagataggc ctggatgaga gtggtggtgg tggcggcagt gaccctggag aggccccac 240
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acgtgctgct cctggggaac ttcgtttctgc acgggggcca ctcagctctg caccagagat 300  
tgtgcacgag gacttgaaga tggggtctga tggggagagt gaccaggctt cagccacgtc 360  
ctcggatgag gtgcagtctc cagtgaagat gcgtatgcgc aaccatcccc caccgaagat 420  
ctccactgag gacatcaaca agcgctatc actaccagct gacatccggc tgcctgaggg 480  
ctacctggag aagctgaccc tcaatagccc catctttgac aagccctca gccgcccgt 540  
ccgtcgtgtc agcctatctg agattggctt tgggaaactg gagacctaca ttaagctgga 600  
caaaactggc gaggtacct atgccaccgt ctacaaaggc aaaagcaagc tcacagacaa 660  
ccttgtggca ctcaaggaga tcagactgga acatgaagag ggggcaccct gcaccgcat 720  
ccgggaagtg tccctgctca aggacctcaa acacgccaac atcgttacgc tacatgacat 780  
tatccacacg gagaagtccc tcacccttgt ctttgagtac ctggacaagg acctgaagca 840  
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gctgctccgt ggctggcct actgccaccg gmagaagggt ctacaccgag acctcaagcc 960  
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ccctgacatc ctgcttgggt ccacggacta ctccactcag attgacatgt ggggtgtggg 1140  
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gagccacgca ccccgacttg atagcgacgg ggccgacctc ctcaccaagc tgttgacagt 1380  
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gtacaaaaag gaggccagcc ttcggtcttc gtcgatgcct gactcaggca ggccagcttt 1560  
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cccacggsca gccagggtc caragctagc ccaggctggg gatctcgact cagacaagat 1980  
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tcagggtca gtccctggat ggggtggttac ctccccttcc tccaccctaa gccctggggc 2700  
cctgaaatgg ggtgggaggg caggggtggg agccctccta gtgggttttg ggggttggt 2760  
tcctgaatgc accataatcg ctgtatgaaa tattaataag tctaaagtga aaaaaaaaaa 2820  
aaaaa 2825

&lt;210&gt; 73

&lt;211&gt; 510

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 73

atgtacgaga gcgcacccaa agaacctagt agagaaaggt attctaacca ctgagaagca 60  
gaatttccts ctatttgaca tgactactca tccagtgacc aatacaacag agaaacagcg 120  
actagtga aaacttcaag atagtgtact agagcggtgg gtaaatgacc ctcagcgat 180  
ggacaagcga acactagcac tctgtgtgct agccactcc tctgatgtgc tagagaatgt 240  
cttctcctct ctgacagatg acaagtatga tgtggcaatg aatcgagcca aggacttagt 300  
agaactggac cctgaagtgg aagggaacaa gccyagtgcc acagaratga tctgggctgt 360  
gctggcagcc tttyaataaa tcytaaagcc rgyrggtggg tttctycttt tcccctgctg 420  
gctggtgact gttcagagac mcccactga gttttgtgtg atgasatgtt ttccatcatt 480  
tttccttyc ttgaatcaga cttgtgaatt 510

<210> 74

<211> 458

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (382)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (388)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (424)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (448)

<223> n equals a,t,g, or c

<400> 74

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ttcaaggtct taaatgttaa atgaaggggt aaaataggaa ggtatttaag taattagcag 120  
gcctcctggg tcttgataac ttcagtgcct ctgggagctg cccggttgcc caccagtctc 180  
tgtggaatcc aggggcctct tcccaatatg gatttgacca gcacttcaat tagtgagttt 240  
ccatkgcat cttagcatta ctctttaata cagacgcctt attttccagg gtttatgaaa 300  
gtttaagtga caaccatgga ttgcaggaac agactgttga gaagctgttt ttccagtgga 360  
aaagttgggt ccaggagatg angggagnct tgaaatagat cctgggatgg aaacataaag 420  
tggnacagcca gattcccatc atgggctncc ccataaaa 458

<210> 75

<211> 377

<212> DNA

<213> Homo sapiens

<400> 75

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gtcctggaaa cacatcaagc tcagctcctg tgtccagctc gcttctctgc tggactcctt 60
gatttttttt ttaatcattg tttgattttg agcagtaacc aggccttttt ttccagatgt 120
tagtccacac ctattcatcc atggaccggc acgatggtgt cccgagccac agctcgcggc 180
tctcccagct gggctcgggtg tcccaaggac cctactcgag cgcgccgcgc ctgtcccaca 240
ccccgtcgtc ggacttccag ccgccctact tcccacccc ctaccagccg ctcccctamc 300
amcagagcca ggacccctac tcccacgtca amgamcceta tccctgaacc cactgcacca 360
gccccagcaa catccct                                     377

```

<210> 76

<211> 2070

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2068)

<223> n equals a,t,g, or c

<400> 76

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tcatgaatgg gaatcctggn cccaagaact ccgcttgcn gacagaggac ctgcagctga 60
ggacctatag cgttgtgcc atgacctnca gtgtatccca gggcaccgcc gtgtgtaata 120
taaagattgg ctgacaaaaa tgtcaggaaa acatgatgtt ggagcttaca tgctaata 180
taagggcgct aatcgtactg aaacagtcac gtcttttaga aaacgagaaa gtaaaagtgc 240
tgctgatctc ttaaagcggg ccttcgtgag gatgagtaca agccctgagg ctttcctggc 300
gctccgctcc cacttcgcca gctctcacgc tctgatatgc atcagccact ggatcctcgg 360
gattggagac agacatctga acaactttat ggtggccatg gagactggcg gcgtgatcgg 420
gatcgacttt gggcatgcgt ttggatccgc tacacagttt ctgccagtcc ctgagttgat 480
gccttttcgg ctaactcgcc agtttatcaa tctgatgtta ccaatgaaag aaacgggcct 540
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caacaccatg gatgtgtttg tcaaggagcc ctcctttgat tggaaaaatt ttgaacagaa 660
aatgctgaaa aaaggagggt catggattca agaaataaat gttgctgaaa aaaattggta 720
cccccgacag aaaatatggt acgctaagag aaagttagca ggtgccaatc cagcagtc 780
tacttgatgat gagctactcc tgggtcatga gaaggcccct gccttcagag actatgtggc 840
tgtggcacga ggaagcaaag atcacaacat tcgtgcccaa gaaccagaga gtgggctttc 900
agaagagact caagtgaagt gcctgatgga ccaggcaaca gaccccaaca tccttggcag 960
aacctgggaa ggatgggagc cctggatgtg aggtctgtgg gagtctgcag atagaaagca 1020

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ttacattggt taaagaatct actatacttt ggttggcagc attccatgag ctgattttcc 1080
tgaacacta aagagaaatg tcttttgtgc tacagtttcg tagcatgagt ttaaatacaag 1140
attatgatga gtaaagtgtg atgggttaaa tcaaagataa gggttatagta acatcaaaga 1200
ttaggtgagg tttatagaaa gatagatata caggcttacc aaagtattaa gtcaagaata 1260
taatatgtga tcagctttca aagcatttac aagtgcgca agttagttaa acagctgtct 1320
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aagcacactc agaaggcttc atcaccaaga ttttgggaga gtaaagctaa gtatagttag 1440
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cttatattta gaaatgactg catttgatat tttaggatat ttttctaggt tttttccttt 1560
cattttattc tcttctagtt ttgacatttt atgatatagatt tgctctctag aaggaaacgt 1620
ctttatttag gagggcaaaa attttgggtca tagcattcac ttttgctatt ccaatctaca 1680
actggaagat acataaaagt gctttgcatt gaatttggga taacttcaaa aatcccatgg 1740
ttgttgtag ggatagtact aagcatttca gttccaggag aataaaagaa attcctattt 1800
gaaatgaatt cctcatttgg aggaaaaaaa gcatgcattc tagcacaca agatgaaatt 1860
atggaataca aaagtggctc cttcccatgt gcagtccttg tcccccccg ccagtcctcc 1920
acacccaaac tgtttctgat tggcttttag ctttttgttg ttttttttt tcttctaac 1980
acttgtattt ggaggtctct ctgtgatttt gagaagtata ctcttgagtg tttaataaag 2040
tttttttcca aaaaaaaaaa aaaaaaantt 2070
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<210> 77

<211> 997

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (619)

<223> n equals a,t,g, or c

<400> 77

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aagtgagggt gtttttcttt ttgttaataa tataaagctg tgtgtttctg attggatgat 960
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```

<210> 78

<211> 1333

<212> DNA



<213> Homo sapiens

<220>

<221> misc feature

<222> (1254)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1297)

<223> n equals a,t,g, or c

<400> 78

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agcgcragct tcggcctcgg ctctgtacca tgaagaaggg cccagtggc tatggcttca 180
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atltggtttc cta                                     1333
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<210> 79

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (542)

<223> n equals a,t,g, or c

<400> 79

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gcttttccat acattgtgtg acccttgccc tatgaccctt tggtgacct taccggaagc 120
catgacgaca gcagcctttt gccattagac gcaggggtgat ggtgaggatt ccaagggtta 180
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gacaaaactg gttaatctga actaggtgac tgttaccttg cgtgttttgt ggccaaacca 240  
ccaccaaaaa cctcacactg tgatgtaagt acttagtgta aaactagtaa acatttttgt 300  
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aacttagcga ggtaaatcga ataaaggagc agtcactctc taacagattg taggagaggt 420  
ttagttggat ttagtctatt tgacttgccc ttaatttaaat tttatggcaa atcacaaatg 480  
tgtcgaaggt ttagcaatat aatagcaaag tcctactcca gtaaataaaa gttggtatgt 540  
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<210> 80

<211> 3203

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1116)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1443)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1942)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3188)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3201)

<223> n equals a,t,g, or c

<400> 80

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gttgctggcg gctgccggtg ctccggcccg gggatacgag acatgcccc aagtgcagcc 180  
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cctggactcg gtcactctcg ccttgctggc agatcccacc cgtcgttca tttacgtgga 360  
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ggacacattt ggcaatgatg ggcgaccccg tgtggcctgg cacattgacc ccttcggcca 600  
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&lt;210&gt; 81

&lt;211&gt; 1710

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1424)

<223> n equals a,t,g, or c

<400> 81

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tgctgctgac cgcggccccc cgcaccacc ccgccggggc ccctgtgcct atgtgccc 180
tggtcgagga gccctggcgg aggcagcgcg ccgttgccct caccacatcg cactggccca 240
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tgtgatggat gaggacgcca ccctccagga ccttcccccc ttctgtgagt cagaccgca 480
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tggtaccagc tcccggccct cgcgccccac ctccacaggt gccttaaagg gccctcgta 1560
cccaagggtg gggcaggggc cctcactctc cggccctggg gtgggggaga gaggaggagg 1620
ttgggggatc ggcagttggg aggggcgctc tgagattaaa gaggttttacc tctgagataa 1680
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1710
```

<210> 82

<211> 1379

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (280)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1365)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1378)

<223> n equals a,t,g, or c

<400> 82

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gtggacgaca cgtgggcaca ggcagaagtg ggccctgtga ccagctgcac tggtttcgtg 180
gaaggaagct ccaggactgg cgggatgggc tcagcctgta tcaaagtcac caaatacttt 240
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tggatcctgg ccgacaagag cagtttcac tctgtcctgc aaacctcctc cagctcgctt 360
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<210> 83

<211> 678

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (602)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (626)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (648)

<223> n equals a,t,g, or c

<400> 83

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cttgtgtgcc tgggtcgggg gctacggggc ccagggattg tgtttaaagt agtgcttcta 120
ccaacatgtc ccgtggttcc agcgccggtt ttgaccgcca cattaccatt ttttcacccg 180
```

```

agggtcggct ctaccaagta gaatatgctt ttaaggctat taaccagggt ggccttacat 240
cagtagctgt cagagggaaa gactgtgcag taattgtcac acagaagaaa gtacctgaca 300
aattattgga ttccagcaca gtgactcact tattcaagat aactgaaaac attggttgtg 360
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ccgatatttc tcaggctctac acacagaatg ctgaaatgag gcctcttggt tgttgatga 540
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antactgtgg ggtttaaagc cactgnagcg ggagttaaac aaactggngt caaccagctt 660
ccttgaaaaa aaagtgga                                     678

```

<210> 84

<211> 2803

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (517)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (572)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1926)

<223> n equals a,t,g, or c

<400> 84

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cttccggtgt catagctgtg ggatccggaa gtaaaaacac aagccccgcs cccrrgaact 480
cgggaaagccg gcgakaagtg tgaggccgcg gtagggncgc atcccgtcc ggagagaagt 540
ctgagtcgcg cagctctgca ggcccgcgga antcgacagc gtcatggcag agcagggtgc 600

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cctgagccgg acccaggtgt gcgggatcct gcgggaagag cttttccagg gcgatgcctt 660  
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gaagatctac cccaccatct ggtggctgtt ccgggatggc cttctgcccg aaaacacctt 780  
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aag 2803

&lt;210&gt; 85

&lt;211&gt; 1278

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 85

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cgaccggcct gggcagcaga cctcagtcac tggcaggtgc tacgtgcagc cccagtrggt 240  
gtttgactca gtgaacgcca ggctccttct ccccggtgga gactacttct ctggggtgca 300  
gctgccccca cacctttcac cctttgtgac cgagaaggaa ggagattacg ttccacctga 360  
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gatgatgaag aagcgggaga agtacctgta ccagaagatc atgtttggca agaggcgaaa 720
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cacacagttg gaccctgat tctcaggggt ctgtgatggg gtgagggtag ggggagcatt 1200
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aaaaaaccca cgcgtccg                                     1278

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<210> 86

<211> 2585

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2573)

<223> n equals a,t,g, or c

<400> 86

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cagcattaca agccaaagcc tcaatccagg gcccttctgt actcctaaag cagggataag 180
gacctatcac ttccgctcca ccttgccga gttccagggt ataatgggca ggaagagagg 240
aaatgtggaa aagggtcgtg tggcaaagct gggaccagat ggtgcagctt tcctgcagat 300
tcccgagaa gagatccctg cctacatgtc tgtgcatcga ctctgagga agctgctaag 360
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aagatacaga ttggtgccca cacagatgac ctgaccaggg ccagcaagct tttccgaggc 720
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cttaatttta attccatctc cagagagatt tgaggtgtat ttaagatgaa aaacaggata 2520
ctacaaagaa acgggaaaac tcaggggttc aagaccagcc taggcaagat ggnaaaaaac 2580
cccccc 2585
```

&lt;210&gt; 87

&lt;211&gt; 385

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (385)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 87

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ttttatattt caactaaaag tatcaaaata tagctttcca gaaaaccccg aaccaaagtc 120
actgactaca tcaaagtcta ctacaccttg agaaaacaaa tgaacgaaaa tctattttcc 180
tcattcatta cccaacaat aataggactc cctatcgtaa ttattatcac tatgtttcca 240
agcattatat tcccatcacc tacccgactr aatcaataat cgactscatc tccattccaa 300
caatgattag tgactgaac atscaaaaca aatrttgatc catgccacaa ccaaaaagga 360
caaactggag cccggatatt gatan 385
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&lt;210&gt; 88

&lt;211&gt; 2500

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (429)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

<221> misc feature  
<222> (1088)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2480)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2482)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2491)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2497)  
<223> n equals a,t,g, or c

<400> 88  
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gccctgctgg tggagaccca gatgaaaaag ttggagatca aacttcggca ctttgaggag 180  
ctggagacta tcatggaccg ggagcragaa gcactggagt atcagaggca gcagctcctg 240  
gccgacagac aagccttcca catggagcag ctgaagtatg cggagatgag ggctcggcag 300  
cagcacttcc aacagatgca ccaacagcag cagcagccac caccagccct gccccaggc 360  
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ccttctgaac agattgggca ggcagggtca actgcagggc cacagcagca gcaaccagct 540  
ggagccccc agcctggggc agtcccacca ggggttcccc cccctggacc ccatggcccc 600  
tcaccgttcc ccaaccaaca aactcctccc tcaatgatgc caggggcagt gccaggcagc 660  
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ccactaaaaa ataaccaatt ttacatttt ttgaggggga gtgagtttta ggaaagggga 1560

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```

<210> 89

<211> 1409

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (841)

<223> n equals a,t,g, or c

<400> 89

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tggaagtaaa ggaaacaggt gatccaggag ggcagctggt gctggcagga gacctcggc 240
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tggarcggct gctcacctac aactccctgt acaagaaggg ccctgatggc tatgacccc 360
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tgacttccta cctgaagctg ctccctggccc cctcctcaa gaagggcaaa gctcgcctga 660
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tgaagacaca gcaccagcc ttctgcacc agccaagcct taactgcctg cctgaccctg 1260
aaccagaacc cagctgaact gccctccaa gggacaggaa ggctggggga gggagttag 1320
aaccgaagcc attyacccck cctccctgct ggggagaatg acacatcaag ctgctaacia 1380
```

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1409

<210> 90  
<211> 1336  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (49)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1284)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1317)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1333)  
<223> n equals a,t,g, or c

<400> 90  
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tactcccgt gcctaccagc aggctctcag cagggtaaa gaagctaagc aaaaaagcca 180  
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gtatagtgcc aatcagaaaa ttcaggatgc tcaggataag ctctacctct catgggtaga 300  
gtggaaaagg agcattggat atgatgatac tgatgagtc cactgtgctg agcacattga 360  
gtcacgtact cttgcaattg cccgcaacct gactcagcag ctccagacca cgtgccacac 420  
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cctttgaatt caataaaatt cactgcagga tagaccagt aaaaaaaaaa aaaaaaaaaa 1260  
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gacgtccaaa gcnccc 1336

<210> 91  
<211> 787  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (677)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (725)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (742)  
<223> n equals a,t,g, or c

<400> 91  
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cgcagatcca gctacctctg ttagccgccc gaagtacaag ttgcagaagc agcttgatag 180  
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acaagtg 787

<210> 92  
<211> 1657  
<212> DNA  
<213> Homo sapiens

<400> 92  
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ggacaatgac tacaggacac aatgtggctg acctggtggt gatactcaag attctgccaa 480

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cggttgaagc tgttgctgcc ctggggaaca aagtcgtgga aagcctaaga gcacaggatc 540
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ctacagtga gattctcatt acaacagtgc caccatctc tcgaaaactg gatccagaac 660
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<210> 93

<211> 485

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (478)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (485)

<223> n equals a,t,g, or c

<400> 93

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<210> 94

<211> 764

<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>  
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<222> (565)  
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<400> 94  
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grtggttgga gaaccaggac cccagagagg tggggccact gaggttggtg cagttgcgct 180  
cactcatcag catggcccgg angtggggg gcatcgggca taccacagca ggcccctatg 240  
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gtttttaaag ataaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 764

<210> 95  
<211> 707  
<212> DNA  
<213> Homo sapiens

<220>  
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<400> 95  
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<210> 96

<211> 815  
<212> DNA  
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<220>  
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<220>  
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<222> (45)  
<223> n equals a,t,g, or c

<220>  
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<222> (50)  
<223> n equals a,t,g, or c

<400> 96  
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<211> 658  
<212> DNA  
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<222> (627)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (634)  
<223> n equals a,t,g, or c

<220>



<221> misc feature  
<222> (635)  
<223> n equals a,t,g, or c

<400> 97  
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<210> 98  
<211> 249  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (248)  
<223> n equals a,t,g, or c

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<210> 99  
<211> 752  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (612)  
<223> n equals a,t,g, or c

<400> 99  
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<210> 100

<211> 3059

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (28)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (109)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (3019)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3047)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3058)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3059)

<223> n equals a,t,g, or c

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&lt;211&gt; 1682

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (52)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 101

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aa

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1682

&lt;210&gt; 102

&lt;211&gt; 938

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (30)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

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<222> (812)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (913)  
<223> n equals a,t,g, or c

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<212> DNA  
<213> Homo sapiens

<220>  
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<222> (1993)  
<223> n equals a,t,g, or c

<220>  
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<222> (2002)  
<223> n equals a,t,g, or c

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<210> 104

<211> 1094

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<400> 104

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ggctgggggg caggtgttgc ttcggcccc gccctccggc cggcgtgtgc gagtgcgccc 180
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ctgggggtga ctttagtttg gggcgggacg ggagccggcg ttgtgactgg cgtggtctgg 480
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ccccamacgc tgctcccgtc ccaccctgcc cgtgctgctg ctctgtgcct gctgtcagag 840  
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gtgagcgggc aagcagagca tccccaccgc tgagcaagaa ctttttcttg tttttaaac 1020  
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aaaaaaaaaa attc 1094

<210> 105

<211> 2297

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (30)

<223> n equals a,t,g, or c

<400> 105

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aaaggaaggc caggggttca catagggccc cagcgagttt cccaggagtt agagggatgc 180  
gaggctaaca agttccaaaa acatctgccc cgatgctcta gtgtttggar gtgggcagga 240  
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tgcttctctc ttgcccagcg ctgggttctc tccaccaggt aggttttctg ttgtggtccc 360  
gtgggagagg ccagactgga ttattctctc ttgtctgac ctgggtcaca cttcaccagc 420  
cagggctttt gacggagaca gcaaataggc ctctgcaaat caatcaaagg ctgcaaccct 480  
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aacagtttgc ccaggaactg ggggatcata tatgtcttag tggacagggg tctgaagtac 2160  
actggaattt actgagaaac ttgtttgtaa aaactatagt taataattat tgcattttct 2220  
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<210> 106

<211> 442

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (419)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (423)

<223> n equals a,t,g, or c

<400> 106

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tatttgcmte gtttttcttg cttgttttcc ccccggttaga ctttgtcggg agagcgcggg 120  
tatgggcccgc aagaagaaga agcagctgaa gccgtggtgc tggatttgta atagagattt 180  
tgatgatgag aagattctta tacaacacca aaaagcaaaa cattttaaat gtcataatg 240  
tcataagaag ttgtacacag gacctggctt agctattcat tgcatgcagg tgcataaaga 300  
gacaatagat gctgtaccaa atgcatacct gggagaacag acatkgattg gaaatatatg 360  
gtatggaarg tattccagaa aaagatatkg atgaaagaag acgacttctt ggaacagana 420  
acnccagaga gtccaaaaaa ag 442

<210> 107

<211> 1019

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (995)

<223> n equals a,t,g, or c

<400> 107

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tgccggtggt tttgtcgttg gcggcggcgg cggcggcggc agcggcggag cagcaggtcc 180  
cgctggtgct gtggtcgagt gaccgggact tgtgggtccc tgcggccgac actcatgaag 240  
gccacatcac cagcgacttg cagctctcta cctacttaga tcccgccctg gagctgggtc 300  
ccaggaatgt gctgctgttc ctgcaggaca agctgagcat tgaggatttc acagcatatg 360  
gcggtgtggt tggaaacaag caggacagcg ccttttctaa cctagagaat gccctggacc 420  
tggccccctc ctcactggtg cttcctgccg tcgactggta tgcagtcagc actctgacca 480



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cttacctgca ggagaagctc ggggccagcc ccttgcatgt ggacctggcc accctgcggg 540
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gctctgggtct gatggcacc agggaagtcc tcacaggcaa cgatgaggtc atcgggcagg 660
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ctccctcac ctttgggtg caggaaactca acctgactgg ctccctctgg aatgactcct 960
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<210> 108

<211> 711

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (642)

<223> n equals a,t,g, or c

<400> 108

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ttgttctctt tgaccatttt cctataatga tgttgatggt caacacctgg actgaatgtc 120
tgttctcaga tcccttggat gttacagatg aggcagtctg actgtccttt ctacttgaaa 180
gattagaata tgtatccaaa tggcattcac gtgtcactta gcaaggtttg ctgatgcttc 240
aaagagctta gtttgyggtt tectggacgt ggaaacaagt atctgagttc cctggagatc 300
aacgggatga ggtgttacag ctgcctccct ctcatgcaa tctggtgagc agtggtgagc 360
gcggggagcc agagaaactt gccagttata taacttctct ttggcttttc ttcactctga 420
aaacaaggat aatactgaac tgaagggtt agtggagagt ttttaattaa aagaatgtgt 480
gaaaagtaca tgacacagta gttgcttgat aatagttact agtagtagta ttcttactaa 540
gacccaatac aaatggatta tttaaaccaa gtttatgagt tggttttttt cattttcyat 600
ttgtatttta ttaagagtgc ttttcttatg gtgatttttt tnaattgcga tttgatatgg 660
tttggccata tggcccccacc caaatcccca tcttgagta taatcccat g 711

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<210> 109

<211> 743

<212> DNA

<213> Homo sapiens

<400> 109

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atttcatatt atataattct gcttattctt tcaaaaattt atacatccat tgggcaagga 180
atggttttca ttaaattacc aatattaaat gcacttaatc attgtgtata ggttaaacca 240
aagtaactat taactaactt ttaggcattt taaggaggtg aaacatacat tttacacata 300
aatatttgat gcaaatatgc agataaaatt ttttaaaat tagaactctg agtaaaacac 360
ctttgataga ttatattggt ttgttttgag agcaaggatt tccagatatg ttcattcttt 420
aaaactca gctttggtt ctttgtttcc caaactgcaa agctgctgat aacaaaactc 480
caggattcca tgtgagttca gctatgtcta cttaacaca aatattaaaa cagaattcag 540
raaatgcagt attaaggatc cagcttctat tgaaaccaat atccatttgc atcataacaa 600
caaacatttg aatgagatgg tcacacttgt acttatcagc aggttccttt aataacaaag 660

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actactaaat gtatatacctt aatcacaaaa gaacaacaaa aaaaatacag gttttttttt 720  
tttcatttcg tacaaaagtc acc 743

<210> 110

<211> 795

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (645)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (737)

<223> n equals a,t,g, or c

<400> 110

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tatttgtatt acaaagaact tgaaatttac tttcttagtt gattatatta aatgatgtat 120  
atattatatg tggtttataa gctcaacact ggccattttt ttagttttat tgtaaattgg 180  
tatttttcta tgtttaatta taatagatct ggctttttct ggatagcata aagatcactg 240  
aactatatat atataagara caagagttct attttagcac aaaggcattt tatattattt 300  
attgaatcca taagtttgtt ttcgtcaaaa acattccata ttattttctgc tcctttttat 360  
ttgtatagtt tgttatttta agaaatggca gtccttctg tcttaatac aataaaattg 420  
aaataatgca cctagtaatg tggccgacat ctcttctcac caccatggac tgttttcaac 480  
aacagttgat cttctgggtct gtgctgagag gcgcatgcat gtctttcgtc acgtcgggca 540  
gcacacctgc tgtgaaatac tgctttcatc tacctcttca gaaggcttct tgcttggtga 600  
caagtaccgc aaaggcttta ttctggactg gctatctcat aaaanggatt tctgtaagac 660  
tttgcagtgt cattccctca gaaccyaggt ttgtttctaa agccacggta ttgtccrrgr 720  
rccctgtgt ktggggncag gtagctatcc ctcccatgac attagtaatc ctttaggatt 780  
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<210> 111

<211> 1332

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (6)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1194)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1237)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1241)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1300)  
<223> n equals a,t,g, or c

<400> 111  
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cctcagacc tccccacatc tgaaactgcc tcccccaac caccagcagc agcaggggccc 180  
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ttagccacc ctcaaaccca gggcccctg gcacctgggc tctggccgtg tttctggcc 300  
agagccccac tttcctaact cgtgctccct tccgcctct tttccgtact gtgaagaaa 360  
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ccagaagaaa cagccccctc tgctgctggg gtgggactgt ctgtgtgccc tgtgggggtc 480  
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gaccccggtc ycacaccac atccagcctg caggcctctc tgcagtcctc tcaccctccc 780  
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ccgccccacc agttaaacgg atgaccaaag acctttctta tgccggaagc aaaaaccaa 900  
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aaggcaaaag ag 1332

<210> 112  
<211> 743  
<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (53)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (272)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (275)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (278)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (590)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (618)

<223> n equals a,t,g, or c

<400> 112

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tgctgtcaac cctttctttg gaagcataat ggatgtcact gaggaggtgt gggacaagct 420
ctggatggac aaggaaaaag aggaagcat gaaagaaacc ctgcgataa gaaggttagg 480
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cactggggaa acagtgggtg tgggtggagg aaccccgctc cgcctctgan ggaccgggag 600
acagcccaca ggccagantt gggctctagc tcctggtgst gtctctgcat tcamccaytg 660
gscttttccc acctygytc amcttactgt tcacctcacc aaatcagttc tgccctgtga 720
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<210> 113

<211> 1690

<212> DNA

<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1659)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1664)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1676)  
<223> n equals a,t,g, or c

<400> 113  
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ccagacacag gccccgagaa gctgccatca ctggagcacc gggactcccc ttggcaccga 180  
ggccccgccc ctgccaggcc taaaatgctg gttatcagtg gaggtgatgg ctatgaggac 240  
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accacctyct cctgtggagg gtgtgaccct gtctgccgtg gcccaggact sgcccgccca 360  
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cagtcagat cggttggggg acatgtgggc tgaccaggac ctctgacct ggagcttcta 600  
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ggggtgattt gaggaatga catgaggaaa agaaacctat tcctgccctg gggaccaccc 840  
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tacagacaca cactgacgca cactgcatgt ccaaggccct aaacattgcc cgttgacata 960  
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aaaaaaaaa 1690

<210> 114  
<211> 620  
<212> DNA  
<213> Homo sapiens

&lt;400&gt; 114

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ttgtaagggg ccatagcctc ttcaggacca actggaggga gagttaggaa acaccagctc 180
ctgcctgggg cagtgaggga atgggagcag ctgtgggcgc ctcatttcag gcaagtcctc 240
cccaaacctt cagatgcagt gagacctggc cttcctgttg tgcttttcag actttgtttt 300
cagaatgctt ttatctcgag tgtgcccttc ggccctcaca agagcccctg gggagtaggt 360
ggtggcctgt gccgtcatcc ccatttcaa gcaggagct gaggtcctgg gaggggaaag 420
tgcttgctg aggtccact gtgttagtg gtgggcagga ctggaactcg gttctccaac 480
agcccagagc tactctttt acaccagag gtggagcagg tggcttaggg ggtggttatg 540
tacttcacaa gccaatccc ttcagccagg agctcctggg tgcatttcg tgtcagaaac 600
agtaccgagt cccacccct 620
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&lt;210&gt; 115

&lt;211&gt; 542

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (392)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (412)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (511)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (521)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (535)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 115

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tcgaccacg cgtccgcttc tcggccctt gtagaacctc tgtcaggctc agcctactcg 60
cctctactcc agcctccact ccggcctcca ccatgtccgt caggtagacc agaagtccta 120
caagggtgcc acctccggcc ccgggcctt cagcagccgc tcctacacca gcgggcctgg 180
ctcccgcac agctcgtccg ccttctcccg ggtgggcggc asttccgggg ggccctgaac 240
agcagcatga gtgtggtcgg gggctacggc ggccggggcc gggtatgggg ggcatcacgg 300
ccgtctcagt gaaccagagc ctgctgagcc cccttwaagc tggaatkagg tcccaacatc 360
```

caagctgtgc gcaacccagg agaaggagca gntcaagacc ttcaacaaca anttggcttc 420  
gttcacgcgac aagtgaagca ctggagcagc agaacaaatt tttggagacc aattggagct 480  
tcttaaagca gcagaagacg cgcggagaac ntagacaaat ntgcgagagt aaatnagaac 540  
tt 542

<210> 116  
<211> 525  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (420)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (424)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (517)  
<223> n equals a,t,g, or c

<400> 116  
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tgctggatgg tgtactggag ggaaaaactga atgcggcggt tattgatgga cccattaacc 120  
atactgccat cgacgggata ccggtatacc gcgaggaact gatgatcgtc acgccacaag 180  
gatatgcgcc agtaaccctg gccagtcagg ttaatggcag taacatttat gccttccgcg 240  
ccaattgttc gtatcgtcgc cacttcgaga gctggtttca tgctgacggt gccgctccgg 300  
gaactatcca tgagatggag tcttatcacg gaatgttggc ctgtgtgac gcaggagcag 360  
gcattgcgct tattccgcgc tctatgctgg aaagtatgcc ggggcatcac cagtgtgaan 420  
cgknggccgt tagctgagca atggcggttg ttaacaacct ggctggtctg gccgtcgtgg 480  
tgcgaaaaaa cgttccgctc gaaggggggc ccggtancca attcgc 525

<210> 117  
<211> 728  
<212> DNA  
<213> Homo sapiens

<400> 117  
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tgacggcagg cgaggaggac gagcagggtc ccgacagcat cgacgcacgc gagatcttcg 180  
atctgattcg ctccatcaat gaccgggagc atccactgac gctagaggag ttgaacgtag 240  
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caaccattcc gcactgcagc atggccaccc ttattggtct gtccatcaag gtcaagcttc 360  
tgcgctccct tcctcagcgt ttcaagatgg acgtgcacat tactccgggg acccatgcct 420  
cagagcatgc agtgaacaag caacttgacg ataaggagcg ggtggcagct gccctggaga 480  
acacccacct cttggagggt gtgaatcagt gcctgtcagc ccgctcctga gcctggcctt 540

tgacccctca gcctgcatac tggatccctg gtcccagctc ctgccagggc tgttacggtt 600  
gttttcttga atcactcaca atgagaaact aacattttgc tttttgtaat aaagttaatt 660  
tatattcarw tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa acccgggggg 720  
gggcccc 728

<210> 118  
<211> 948  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (920)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (944)  
<223> n equals a,t,g, or c

<400> 118  
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agcagaagag gaagcctggg ctgcggcgga gcccatcaag aaagtccgga agtctctggc 180  
tcttgacatt gtggatgagg atgtgaagct gatgatgtcc aactgcccc agtctctatc 240  
cttgccgaca actgcccctt caaactcttc cagcctcacc ctgtcaggta tcaaagaaga 300  
caacagcttg ctcaaccagg gcttcttgca ggccaagccc gagaaggcag cagtggccca 360  
gaagccccga agccacttca cgacacctgc ccctatgtcc agtgccctga agacggtggc 420  
ctgcgggggg accagggacc agcttttcat gcaggagaaa gcccggcagc tcctgggccc 480  
cctgaagccc agccacacat ctgcgaccct catcttgtcc tgagggtgtg aggggtgtcac 540  
gagcccatc tcatgtttac aggggttgtg ggggcagagg gggctctgtga atctgagagt 600  
cattcaggtg acctcctgca gggagccttc tgccaccagc ccctccccag actctcaggt 660  
ggagcaacag ggccatgtgc tgccctgtg ccgagcccag ctgtgggcgg ctccctggtgc 720  
taacaacaaa gttccacttc cagggtctgcc tgggtccctc cccaaggcca caggagctc 780  
cgtcagcttc tcccaagccc acgtcaggcc tggcctcatc tcagaccctg cttaggatgg 840  
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aaaattgcct ctctctttgn aaaaaaaaaa aaaaaaaaaa gggngggc 948

<210> 119  
<211> 211  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (123)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (125)



<223> n equals a,t,g, or c

<400> 119

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tcgacccacg cgggtccgctt ggtgggggtcg gctgctttct cgcgtttccc cccaaccccg 60
tcgggctctg cccagcgctt ccacgcgga ccaactgcca gaggcgcggc gcggcgctga 120
gcngngcgag tgtgaggaaa ccgccgcctc agccgagcgc gcggggccgc ccaggcgctt 180
agttttcggc gcgcagtcgc ggtcccccgg c 211
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<210> 120

<211> 1308

<212> DNA

<213> Homo sapiens

<400> 120

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gctgctctgt gaaggaaccg cctttctctc cgcgtgtctc acccttttct ccccatatct 120
gtttggacat gagctgaggg cacggtcgcg ggcggtcagc ctgttcgcag ctacggcgag 180
gaggggcgcg attgytcctt gttgccgctc cgttagtggt ccgcgtccat tccgcgcggt 240
gtcccgatth tagggtagg gagaagtgtc agcttcaggc atcgcgaggc gtggcgggccc 300
catggccccc ctgggaggcg ccccgcggtt ggtactgctg ttcagcggca agaggaaatc 360
cgggaaggac ttcgtgaccg aggcgctgca gacgagactt ggagctgatg tctgtgctgt 420
cctccggctc tctggtccac tcaaggaaca gtatgctcag gagcatggct tgaacttcca 480
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caggaggaga ctccaagggc aaaggagggt gtcttgctg tgcttgaagg cgaaacctg 1140
ccatatcccc agtgccagtc cctcagcct gtggtggcct tgcacctga ctggatgttc 1200
tcagcccctt gttctgggca agaaccaga gctccccagt gtggatacta ataaacctct 1260
tggagcacia aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaagg 1308
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<210> 121

<211> 2516

<212> DNA

<213> Homo sapiens

<400> 121

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ctattgaaat cacaaaagta gaacagggcw ytttattttt gtataattta ggattaggtta 180
tgcttctttg ttctaacaag tcatgttttc taacctttct ttcactaagc aaaccagaac 240
agatttgaac tgttatgggt tatatattag tatggagatc agctcagatg acattaaaaa 300
tgccgtagtg ttattcttgt atgccaaatc ttttttccc caaaattagc actttaattt 360
tatttactgt tataatattt gttttcttag attaggtag aaatcttaat ttggccaccg 420
cctactttga caagtaaata ttacatcata cgattttgca acattaaatt agaactag 480
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aaactaaaaa attatgtttc agtgaatgct acaactaagc attttttttt ttttaagaaaa 540
acaattgtat tatgttttgt tgccttgcca ctttgagtat cttatctgaa aatctgttcc 600
tgccatgtt tttctcctgt taacataaac tatgtgccct gtgaatttct ggggactgaa 660
tttgaaattg ctccctgcca cgttttggtg cctggcgtgt atctgaatgc ctgaatatct 720
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<210> 122

<211> 1139

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1053)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1124)

<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (1125)  
<223> n equals a,t,g, or c

<400> 122  
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ctgccctctg acctctcccc tagcaggcga ccatggggaa cgtgttggt gccagctcgc 180  
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<210> 123  
<211> 2114  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1966)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2039)  
<223> n equals a,t,g, or c

<400> 123  
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gcgccgaccc aagcgatctg gagagcggcg ggctgctgca tgagattttc acgtcgccgc 180  
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gtgcccgaa aaatgattaa agcattcagt ggaagtatat ctatttttgt attttgcaa 720  
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tgagcacttg ctataagttt ttttaattaac atcactagt acactaataa aattaacttc 840  
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tagtgagtcg tattataagc taggcactgg ccgtcgtttt acaacgctgt gactgggana 2040  
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<210> 124  
<211> 583  
<212> DNA  
<213> Homo sapiens

<400> 124  
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ttgtgactgc acaccgggac ccactcaat tcaaagacc agactgcttc aaccctacca 180  
acttcttgga caagggaag ttccagggca atgatgcttt catgcccctt gcctcagggt 240  
caggcagagg aggaaggga ccagcctgga ctggctctgg ggtacctggt gctcactgtg 300  
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gccagtggcc tgctgaggtc aggctccact atggtgggct cactggccct caaacctcca 540  
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<210> 125  
<211> 1987  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature

<222> (7)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (14)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (517)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1960)  
<223> n equals a,t,g, or c

<400> 125  
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caagagcaag gaagacctgg tgtcccaggg cttactgaa ttcacaattg aggatattcca 660  
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cggtgat 1987

<210> 126

<211> 1451

<212> DNA

<213> Homo sapiens

<400> 126

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cgtccgtggg aattaaagct gcaaatggtg tggattagc aactgagaaa aaacagaaat 180  
ccattctgta tgatgagcga agtgtagaca aagtagaacc aattaccaag catatagggt 240  
tggtgtacag tggcatgggc cccgattaca gagtgttgt gcacagagct cgaaaactag 300  
ctcaacaata ctatcttgtg taccaagaac ccattcctac agctcagctg gtacagagag 360  
tagcttctgt gatgcaagaa tatactcagt caggtggtgt tcgtccattt ggagtttctt 420  
tacttatttg tggttggaat gagggacgac catatttatt tcagtcagat ccatctggag 480  
cttactttgc ctggaaagct acagcaatgg gaaagaacta tgtgaatggg aagactttcc 540  
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ccctaaagga aagctttgaa gggcaaatga cagaggataa catagaagtt ggaatctgca 660  
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aaaaaaaaa a 1451

<210> 127

<211> 1234

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (857)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1204)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1226)

<223> n equals a,t,g, or c

<400> 127

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gtgtattttg tacacaggtt ttatgctggg ggctcagaga gaagtggaca gcagattgtt 180
ggccctccca ggaagaaaag tcccaacgag ctggtgggat gatctcttta aaggtgccaa 240
agagcatgga gctgtagctg tggagcgagt gaccaagagc cctggagaga ccagtaaacc 300
gagaccattt gcaggaggtg gctaccgcct tggggcagca ccagaggaag agtctgccta 360
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gaagagtgga ttcagcctgg ataatggaga actcagaagc taccaagacc catccaatgc 480
ccagtttctg gagtctatcc gcagagggga ggtgccagca gagcttcgga ggctagctca 540
cggtggacag gtgaacttgg atatggagga ccacgaggac gaggactttg tgaagcccaa 600
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ctggtgcaga aatttaacca cagccacagg atcagcgaca tccgactctt catcgtggat 840
gcccgccag ccattgntgc caccagcttt atcctcatga ctactttccc gaacaaagag 900
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aacgtctcct ccattagctc gggttcttag atcttggtg gacgtttgtt ttctccttag 1140
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accnaaaggg gggcccgtc ccaatncccc cctt 1234
```

<210> 128

<211> 863

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (840)

<223> n equals a,t,g, or c

<400> 128

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cgtgggtatt agggacatct cggccgtcct gaaggacccc gcctccttcc gcgccgccat 180
cggcctcctg gcgcgacacc tgaaggcgac ccacgggggc cgcacgcact acatcgagg 240
cctagactcc cgaggcttcc tctttggccc ctccctggcc caggagcttg gactgggctg 300
cgtgctcatc cgaaagcggg ggaagctgcc agggcccact ctgtgggcct cctattccct 360
ggagtacggg aaggctgagc tggagattca gaaagacgcc ctggagccag gacagaggg 420
ggtcgtcgtg gatgatctgc tggccactgg tggaccatg aacgctgcct gtgagctgct 480
gggccgcctg cagctgagg tcctggagtg cgtgagcctg gtggagctga cctcgcttaa 540
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cagtgaccag gggcaccggc tgcccacagg gaacacattc ctttgctggg gttcagcgcc 720
tctcctgggg ctggaagtgc caaagcctgg ggcaaagctg tgtttcagcc acactgaacc 780
```

caattacaca cagcgggaga acgcagtaaa cagctttccc acaaaaaaaaa aaaaaaaaaan 840  
aaaaaaaaaa aaaaagggcg gcc 863

<210> 129

<211> 1238

<212> DNA

<213> Homo sapiens

<400> 129

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ccctccctgc ccctgcccta gctgctgtgt gttcagttgc cttctttcta cctcagccgg 180  
cgtggagtg tctctgtgca gttagtgcc cccacacac ccgtctcttg attgagatgt 240  
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gctggcgctc tccctcagca caggtgggtc agtggccagc aggcccatct ggagtgggag 360  
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cttaacatcc ttatctgtgt ccgccacgga ggtgactgag ctgctagcga gttgtcctgt 660  
cccagtgact tgagttttgg aaaagctgac tcacgcccat ccatttcaca gcccttcct 720  
ggggacagtc gcttccgct tgacacctca ctctcagttg aataactcaa gcttggatcat 780  
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tctgtcctgt tggtgcttg cttccagctc cccccaatct ccacgcagc gggttcctcc 1140  
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attctyawca agaagattta tgaggagaag aaaaagaa 1238

<210> 130

<211> 379

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (373)

<223> n equals a,t,g, or c

<400> 130

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gggggtagga gcagagcctg cscatctgga ggcagcatgt ccaagaaagg gagtggaggt 120  
gcagcraagg acccaggggc agagccacgc tggggatgga cccttctcag gacacgctgc 180  
ggyggctgcg tgaggccttc aactgagggc gcacgcggcc ggccgagttc cgggctgcgc 240  
actccagggc ctgggccact tccttcaaga aaacaagcar cttctrcgm acgtgctggc 300  
ccaggaactg cataagccag ctttcgaagg cagacatc tgaatcatcc ttgcccagaa 360  
cgaggttgaa tangctctt 379

<210> 131



&lt;211&gt; 1786

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 131

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cctgggcgct aagatggcgg cggcgtgagt tgcattgtgt gtgaggatcc cggggccgcc 60
gcgtcgctcg ggcccccca tggccgtcac catcacgtc aaaacgctgc agcagcagac 120
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catggtgacc aagaccaaag ccggccaggg tacctcagca cccccagagg cctcaccac 360
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attgtcaagg ccacccccac ccagaaacag aaccgtgtct ctgataaagg ttttgaagtg 1740
aataaagttt taaaaactaa aaaaaaaaa aaaaaaaaa aaaaaa 1786
```

&lt;210&gt; 132

&lt;211&gt; 974

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (165)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (853)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (963)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 132

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tgaagytgat gatgtccaca ytgccaakt ytttatcctt ggcgacaayt gcccttgca 960
aanttttcca gcct 974
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&lt;210&gt; 133

&lt;211&gt; 634

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 133

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cagtgccctt tccaggcctt aagagaagta aaacttagct gcagcgtcag gaggtggacc 180
ccagagtgtg agtggcacgc ttctctgtga acccgctcct accatgtttg ccacatctgg 240
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gcgcttcccg cacctcccg cgctgtgtct acaccggcg cgccagcatt tgccagagcg 600
gccccgscgy tgcccgctgt gcgycctcag gttt 634
```

&lt;210&gt; 134

&lt;211&gt; 1855

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1818)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1845)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 134

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ggcgaggggc tgcagtgcgt ggtgcccttc ggggtgccag cctcgccac ggtgcggcgg 120
cgcgcgagg ccggcctctg tgtgtgcgcc acagcgagcc ggtgtgcggc agcgacgcca 180
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&lt;210&gt; 135

&lt;211&gt; 917

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (913)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 135

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<210> 136

<211> 1271

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1236)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1255)

<223> n equals a,t,g, or c

<400> 136

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<210> 137

<211> 2017

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (295)

<223> n equals a,t,g, or c

<400> 137

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<210> 138

<211> 937

<212> DNA

<213> Homo sapiens

<400> 138

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<210> 139

<211> 2759

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (171)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1654)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2743)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2744)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2746)

<223> n equals a,t,g, or c

&lt;400&gt; 139

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&lt;210&gt; 140

&lt;211&gt; 1241

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (317)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 140

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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa g 1241
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&lt;210&gt; 141

&lt;211&gt; 3405

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1569)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 141

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&lt;210&gt; 142

&lt;211&gt; 2268

<212> DNA  
<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2196)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2232)  
<223> n equals a,t,g, or c

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gccgaagacg tgcctaccc taccacaagg gctgtgtctc taccacctag cctgggaggt 180  
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gcgcttccat cctaaagcca taatgaaaat atcttcctct cttcccccatt ctatacaaaa 420  
tactaagtgg ttttcttgcct cccactccct accccttagt taaatagggt ttattttcca 480  
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&lt;210&gt; 143

&lt;211&gt; 1757

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 143

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attttcacac acagtgtctga agatgtctga agaccaaaac atagctcata aaatcagggtc 180  
ctgagatagt taccataaaa gaggaatcct ttgagtgtat gccattggtg agccgatgag 240  
catggaccat agaagggtc aatgtagaag gtaaaatttg caaatcataa ttgagaaata 300  
tgaaatgtat tcccatatcat aatatgggtat aggggtgtaat gtacctgctt ttgatcactt 360  
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agttgtagat tgcattttta taaaaaaaaa tacagataga ttgatgataa tagatattgg 600  
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tgagccagtt gatttgaatg cattggatat tagtgttaga aacaatgtat agtttagatt 780  
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taagacagct tagtggtgtg atacttagaa ttctatggtt tgatgtttct tttagaaatg 900  
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aaaaaaaaaa aaaaatt 1757

&lt;210&gt; 144

&lt;211&gt; 1062

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

<222> (52)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1056)  
<223> n equals a,t,g, or c

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gaggggggag gaaagaagaa agggggcggg gttgaggggg gcgggcctgg acctggggag 180  
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ggccaagccg tgtgggggtg gcctgagcgg ggaagcccgc aaacaggtgg aggtcttcag 300  
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaanaaaa aa 1062

<210> 145  
<211> 1030  
<212> DNA  
<213> Homo sapiens

<400> 145  
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cgcggtctcc agccacacca agttcagcat ttaccctccc attccaggag aggagagctc 240  
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caacaacaca cagatccagg tagtctctgc tagtaatgag ccccttgccct ttgcttccctg 360  
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aaaaaaaaaa

1030

&lt;210&gt; 146

&lt;211&gt; 814

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 146

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aactaccggc tcaaggaata cgagaaggcc ttaaagtacg tccgcgggtt gctgcagaca 420  
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ggactcatcg gacttgctgt gtccaagtcc aaatcctgaa ggagacgcgg gagcccacgg 600  
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ccgtctctat cctctgtggc cttcagctaa tttctgtctc cctgagattc gtccttcagc 720  
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aaaaaaaaaa aaaaaaaaaa aaaaaagggg gggg 814

&lt;210&gt; 147

&lt;211&gt; 2678

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 147

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&lt;210&gt; 148

&lt;211&gt; 1028

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 148

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agccttttga caacatacag gcattctttt aaaaccaggc tgaaacattt tatttccgag 360  
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ttggttca 1028

&lt;210&gt; 149

&lt;211&gt; 1425

<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (647)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1359)  
<223> n equals a,t,g, or c

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tacaaaaaaa aataccggaa tctgaagcgg aagctcaagt tcctcatcta cgagcacgag 180  
tgcttccagg aggagctgag gaaagcgcaa aggaaattac tgaagggtgc ccgggacaag 240  
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gatgccactg catcatcaga taacagcgag acggagggga caccacaagt gtctgacaca 360  
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tccttgccctc cttcaacagg gtttcccctt caggcctccg gggctccctc cccatacctg 480  
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cgtaaactag cacgggtgtc cccagggagg gtgcaggggc cctgccttca aacccccggc 1020  
ccctccaggg gacagttatt taaacgagtg gccgggagca tctgccacct gctggggagg 1080  
cagagacctt gcaatggcca cctctttaaa agggcagctg tacagggcta ggttttttca 1140  
atgaagtttc tgatttaaag gagtggctct gggtttgtt tttgtcctt ttttttgaga 1200  
cattctctc ctctgaacct cccctaattc gacctctcc ctgttggggg agagggacgg 1260  
ggcagcgtgg agaggcagga gtgaggagcg cgggggcctg gggccgggct ctgagcactg 1320  
cccgggtgtg cagatgatgg ggggtttgca tatttgang ggactagcga gtcaggcagg 1380  
aggtttgcag atgtgaatat agaactccgc agccccctcat gagca 1425

<210> 150  
<211> 780  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (285)  
<223> n equals a,t,g, or c

<400> 150  
gctgcgagaa gacgacagaa ggggagagcc aatggaaaagg ggctgccgcg cggccgtaaa 60

gagttttag agcagttcgg gtgcggtacg ttgcattccg gtaccggacg ccgagagcgg 120  
tttgtctccg tctctggagt tgtaggcgag aggtgatcat gtccggtcgc gggaaacagg 180  
gcggcaaaagt gcgagcaaaag gccaaatccc gtcctctccg cgcgggcctg cagttcccg 240  
tgggccgagt gcacagactg ctgcgcaaaag ggaactacgc ggasnagtgg gcgccggggc 300  
gccggtgtac ctggcggcgg tgttgagta ctttacggcg gagatcctgg agctggctgg 360  
caacgccgcg cgtgacaaca agaagaccag gataattccc cgccacctgc agctcgccat 420  
ccgcaacgac gaggagttaa acaagctgct gggcaaagtg accatcgctc agggcggcgt 480  
cctgcccac atccaggccg tgctgctgcc caagaagacg gagagtcaga agacgaagag 540  
caaatgacct tgacgccgcc ctcaaggagc tggctccscg agcaaaggcc cttttcatgg 600  
tcgtcccga atgtttttga atgtgctgga tgtcatggag ggccggtgac atctagcggg 660  
gaggtgggcg gcgaggggtcc cggcgggagc caataaagtt ggtgaaaatc gtaaaaaaaa 720  
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

<210> 151

<211> 1066

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1061)

<223> n equals a,t,g, or c

<400> 151

ggacccgcc a tggcgcgga gaaggtgcgt ccgcggctga tcgcggagct ggcccgcgc 60  
gtgcgcgccc tgccggagca actgaacagg ccgcgcgact ccagctcta cgcggtggac 120  
tacgagacct tgacgcggcc gttctctgga cgcgggctgc cggctccggc ctgggccgac 180  
gtgcgcgcg agagccgcct cttgcagctg ctccggccgc tcccgtctt cggcctggg 240  
cgccgtgtca cgcgcaagtc ctggctgtgg cagcacgacg agccgtgcta ctggcgccctc 300  
acgcgggtgc ggcccacta cacggcgag aacttgacc acgggaaggc ctggggcatc 360  
ctgaccttca aagacgcctc tttttcttca tcagggaaga ctgagagcga aggcgcggga 420  
gatcgaacac gtcattgtacc atgactggcg gctggtgccc aagcacgagg aggagccctt 480  
caccgcgttc acgcgcgcg cgaagacag cctggcctcc gtgcggtacc cgcctctcct 540  
ccggggccatg attatcgag aacgacagaa aaatggagac acaagcaccg aggagcccat 600  
gctgaatgtg cagaggatac gcatggaacc ctgggattac cctgcaaac aggaagacaa 660  
aggaagggcc aagggcaccc ccgtctagaa tgccagaacc agcgggtggc cttaggggct 720  
gtgaggcagt ggggacctta ttgatgaaag aaaccgtctt tgcgttacac ccgagctctg 780  
ctctcgagc agggagctca ccttcgcga cgtgttctga gggctctgcat cttagggggg 840  
agggctgggg caaatcgcca cctgtgcctt tcctctggcc ctgctgcccc cacacccaac 900  
tccgagggcc cagctgggg aaagcgggaa gcgctcgctc cttttcccc attagtgtc 960  
tctctgcctg gatcccgga gaagctatga aagggaataa agagaaaaga artamaaaaa 1020  
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nccccct 1066

<210> 152

<211> 1649

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1543)



<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1579)

<223> n equals a,t,g, or c

<400> 152

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accccggtc tccaaggagg tgtgacatca tcatcatctc tggccgaaa gaaaagtgtg 60
aggctgcca ggaagctctg gaggcattgg ttctgtcac cattgaagta gaggtgccct 120
ttgaccttca cgtttacgtt attgggcaga aaggaagtgg gatccgcaag atgatggatg 180
agtttgaggt gaacatacat gtcccggtcac ctgagctgca gtctgacatc atcgccatca 240
cgggcctcgc tgcaaatttg gaccgggcca aggctggact gctggagcgt gtgaaggagc 300
tacaggccga gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc 360
ccaaatacca tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg 420
agcatgacgt gaacatccag ttctctgata aggacgatgg gaaccagccc caggacccaa 480
ttaccatcac aggttacgaa aagaacacag aagctgccag ggaatgctata ctgagaattg 540
tgggtgaact tgagcagatg gtttctgagg acgtcccgct ggaccaccgc gttcacgccc 600
gcatcattgg tgcccgcggc aaagccattc gcaaaatcat ggacgaattc aaggtggaca 660
ttcgcttccc acagagcggg gccccagacc ccaactgctg cactgtgacg gggctcccag 720
agaatgtgga ggaagccatc gaccacatcc tcaatctgga ggaggaatac ctgactgacg 780
tggtggacag tgaggcgctg caggtataca tgaaccccc agcacacgaa gaggccaaag 840
caccttccag aggttttgtg gtgcgggacg caccctggac cgccagcagc agtgagaagg 900
ctcctgacat gagcagctct gaggaatttc ccagctttgg ggctcaggtg gctcccaaga 960
ccctcccttg gggccccaac cgataatgat caaaaagaac agaaccctct ccagcctgct 1020
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aaattgttga cgctcttccc ccttcccagag gtccgcaggg agcctagcgc ctggtgtgtg 1140
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taaaccaagg tcatgacat tcgtgctaag ataacagact ccagctcctg gtccaccggg 1260
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cttctgtgt catgacctca ggaaataaac gtcttgaact ttataaaagc caaacgtttg 1380
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gaagacctgg caatggacag caggaggcag gttcctggag ctngggggtg acctgagagg 1560
cagagggtga cgggttctna ggcagtcctg attttacctg ccgtggggtc tgaaracc 1620
aagggtccct gacctacct ccaactgcca 1649
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<210> 153

<211> 660

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (35)

<223> n equals a,t,g, or c

<400> 153

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ccggaaattc ccgggtcgac ccacgcgkcc gcggnagwgc tcacacgtgt gctccctgcc 60
ctgctcctgg ccccttgccc ggccgggctg tttctggcca tgggtcgtc ccgccggaca 120
ggcgcgcacc gagcgcactc tctagcccg cagatgaagg cgaacggcgg cgcccgact 180
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tggatgagat tcaccgagag ctgcggcctc agggatccgc acgaccccag cccgacccaa 240  
 acgccgagtt cgaccccagac ctgccagggg gcggtctgca ccgctgtctg gcctgcgcga 300  
 ggtacttcat cgattccacc aacctgaaga cccacttccg atccaaagac cacaagaaaa 360  
 ggctgaagca gctgagcgtc gagccctaca gtcaggaaga ggcggagagg gcagcgggta 420  
 tgggatccta tgtgcccccc aggcggctgg cagtgcccac ggaagtgtcc actgaggtcc 480  
 ctgagatgga tacctctacc tgacatggcc tgaagatgca ggcagagga attgcccatg 540  
 gacagtgacg caaggactag gctgggaggg agcgtgccaa ccccttttgc ctctgggttt 600  
 ggggagcgga gggcctcttc ttggtgccct gcccacaata aaggaactgg acaaagagaa 660

<210> 154

<211> 605

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (449)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (574)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (578)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (583)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (587)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (596)

<223> n equals a,t,g, or c

<400> 154

ggagagctc caccttccat ccggcgccgg ctttcggcgc gacggtcgcc gcgttccatc 60  
 gtcgcgcggc ccttcgggag ccgagcccc caatgtcggg ccccaacgga gacctgggga 120  
 tgccgggtgga ggcgggagcg gaaggcgagg aggacggctt cggggaagca gaatacgtg 180  
 ccatcaactc catgctggac cagatcaact cctgtctgga ccacctggag gagaagaatg 240  
 accacctcca cgcccgcctc caggagctgc tggagtccaa ccggcagaca cgcttgaggt 300  
 tccagcagca gctcggggag gccccagtg atgccagccc ctaggctcca agagcccca 360

accgggaccc aacctgcct ccctgggcta ggctctggcc tgggcaactca mccccctggct 420  
tagacamctt ctcaagggt- ggccttcang gacctctgggt gggctctgcct gcctgggcca 480  
accttctctgc ctgggscctc ccttggctam ctgggscagc ccccaaccaac tggcatgccc 540  
tcttgggggc caaagaatgg ggcttgaac ccancantt gctgcncaa cccaanttcc 600  
tggggg 605

<210> 155

<211> 695

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (173)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (499)

<223> n equals a,t,g, or c

<400> 155

gaaccctaga aaaaaggatg cagtactaaa gtgtcattca ttcaaagcca ctctcttttt 60  
ggtattccac ccattttcca gacggtgaca ctgagggtca ggaagcagta gggacttgca 120  
caaagccctt tgggaagcag gctgggaaac agtggaggga ggggtgccat tanccccaag 180  
gagacacagg atctgggctc tktytttsgc ctctctccca gaatacgctg ccatcaactc 240  
catgctggac cagatcaact cctgtytgga ccacctggag gagaagaatg accacctcca 300  
cgcccgctc caggagctgc tggagtccaa ccggcagaca cgcttgaggt tccagcagca 360  
gctcggggag gccccagtg atgccagccc ctaggctcca agagcccca accgggaccc 420  
aacctgcct ccctgggcta ggctctggcc tgggcaactca cccccctggct tagacacctt 480  
ctcaagggtt ggccttcang gacctctgggt gggctctgcct gcytgggcca cccttctgc 540  
ctgggrrctc cccttgkcc tactggggcc agccccacc acctggcatg ccctctggg 600  
gccaaagatg ggcttgaam ccaccattg sctgccaac caattcctgg gcytcccca 660  
wtytgcccag gcttgaatgt tcacatgaaa tgggt 695

<210> 156

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<400> 156

cggtgggctc gcgttgaggc tgcggtcatg gagggagcag gagctggatc cggttccgg 60  
aaggagctgg tgagcaggct gctgcacctg cacttcaagg atgacaagac caaagtgagc 120  
ggggacgcgc tgcagctcat ggtggagttg ctgaaggctt tcgttggtga agcagcagtc 180  
cgcggcgtgc ggcaggccca ggcagaagac gcgctccgtg tggacgtgga ccagctggag 240  
aagggtgctt gcagctgctc tggacttcta gggatctcag ccgtggckna ggccaccccc 300

agaggagccc ctggtccaca gaagcaggcc ttgtgtttcc agcggcctct gataagaggc 360  
aggggaaggam ctgaaggatt tggarttgat tcaaacaaga tctctgggag tctccagcct 420  
gtgcagaagg ggcaggactg cagtgcactg cgggccttgg agtgtccagt ggggacactg 480  
gtgtgggaag gggcagcacc tggggagtcc ctgcctctcc tccctgggac aatagtgtgc 540  
atgccacccg gggctctaca ggcaggtgct gggaaaggcc tggccagcag gtagcctgtg 600  
tgtttgacaa acagcagctg gcagcgtgc ctctgccc cattcctgcc acccgacatc 660  
aaagctggcg tgtgaccttt ccagccatgc gatattcccc ttggaagatg cttccccagg 720  
ctataaattt gttctcacia agcaacatca ataatcaaa actgtctcty ccaaaaaaaaa 780

<210> 157

<211> 1127

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1113)

<223> n equals a,t,g, or c

<400> 157

aacttcagtg ccctcactgt agaatttaaa agccttactg ttgattgccc atggtggact 60  
tgatggagaa attaaatata ttctattatg ctttcaaaa tactgtatat gtttcagcaa 120  
gtttggggaa tgggagagga caaaaaaag ttacatttaa tctatgcatt ttgccaagc 180  
catattgagt tattttacta ctagagacat taggaaacta actgtacaaa agaaccaagt 240  
ttaaaagcat ttgtggggtt acatcatttc tataattgta taatgtatct cttgtgggtt 300  
ttaaatgata aagacattaa gttaacaaac atataagaaa tgtatgcact gtttgaaatg 360  
taaattattc ttagaacact ttcaatgggg gttagcattgt ccttttagtg ccttaatttg 420  
agataattat ttactgcca tgagtaagta tagaaatttc aaaaaatgta ttttcaaaa 480  
attatgtgtg tcagttagtt ttctattgat aattggttta atttaaaata tttagaggtt 540  
tgttggactt tcataaattg agtacaatct ttgcatcaaa ctacctgcta caataatgac 600  
tttataaaaac tgcaaaaaat gtagaagggt gcaccaacat aaaaaggaaa tatggcaata 660  
catccatgat gttttccagt taacatagga attaccagat aaatactgtt aaactcttgt 720  
ccagtaacaa gagttgatcc atatggacag tatgatttat tgtttatttt tttaaccaa 780  
tacctcctca gtaatttata atggctttgc agtaatgtgt atcagataag aagcactgga 840  
aaaccgatcg tctctaggat gatatgcatt tttcaagtgg tattgaaagc cgcactgatg 900  
gatatgtaat aataaacata tctgttatta atataactaat gactctgtgc tcatttaatg 960  
agaaataaaa gtaatttatg gatgggtatc tttaattttt actgcaatgt gttttctcat 1020  
ggctgaaatg aatggaaaac atacttyaat tagtctctga ttgtatataa atgtttgtga 1080  
aattccatgg ttagattaaa gtgtrttggg aanaattctc catggggg 1127

<210> 158

<211> 1282

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (120)

<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (205)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (207)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (236)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (732)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1279)  
<223> n equals a,t,g, or c

<400> 158  
tgctctacaa atagtaaaa taaaaataa aaaaagtagc tgggcgtggt ggtgtgcacc 60  
tgtggtccca gctgcttggg atgctgaggt ggaaggatct cttaaaccce ggaggggtggn 120  
aggctgcagt gaacttgcga ttgcaccact ggcactccag tctgggggac agagtgcagac 180  
cccatctcaa aaaagtgttt aattnantat acttgtgagt ggtctatttg catttnaaaa 240  
ctgctttcta gaattaggat agctccctta ggtttaatgt tttgggtgagc aggaatatca 300  
gttacccttc cagatcttaa ttctagtgtt ttatcactt tttcatgagg tgatctcatc 360  
ctcatctcct agcatgtctg gcaattttga tttctgaact ctgtgctacc tcagaggcca 420  
gcttccttag ggaaaaatca gtgctgaaat aaagtatat ttccttttct gctctaaata 480  
tatagtgggg gaataagaga aatgaagagg aattcctgag aacgtaatta ctagaaactc 540  
ccctctccca cgtaatgtct ctacacacacc atggaccctt attcccccaa tttgcgaccc 600  
cccacccac cccacaacag gtggtgatct ttgtgaagtc tgtgcagcgg tgcattgcct 660  
tggcccagct actagtggag cagaacttcc cagccattgc catccaccgt gggtgcccc 720  
aggaggagag gntttaaga ttttcaacga cgaattcttg tggtaccaca cctatttggc 780  
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tttgcatcac caccactcct gaacccccat ttctgatttg tcagaatttt tttttaacaa 1200  
aactaaaaat gaaacacatg tgtctgtggt atctaaaaaa aaaaaaaaaa aaawwggggg 1260  
gsggcccgtc cccattggnc ct 1282

<210> 159  
<211> 1505  
<212> DNA

<213> Homo sapiens

<400> 159

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ttacatgttg cagaagctaa ttgaagagac agatagggttt gtagtggttca cagaagagga 60
atcaggcatg agtgaccagt tgtgtggcat tgctgcctgc cagacggatg acatatacaa 120
ccgaaactgc cttattgaat tggtaacct gtcagatggt tcttcgtgga gcagagacak 180
aaggctgtgt catttgttca gctgccaaag cccaactgct gcagtgccag caccatccag 240
cctggatggt tgatacattg aagcaaaaga catcctggac ttgcctcttg gatggcatgc 300
agtactttgc caccactgaa agcagcccca cagagcagga tggccgacag ctctggttag 360
aggtgaagaa tatcgaggag caccggcagc gtagtctgga ctctgtgcag gagctgatgg 420
agagtgggca ggcagtgggc ggcagtgtta ccacaaccac agattggaac cagccagctg 480
aggcacagca agcccagcaa gtccagcggg tcatctcgcg ttgcaactgc cgaatgtact 540
atattagtta cagccatgac attgatcctg aactagcaac tcagattaag ccacctgaag 600
ttcttgagaa ccaggaaaag gaagatctcc taaagaagca ggaaggggct gtggatacct 660
tcacccttat ccaccatgag ctggaaattt ccaccaacct agctcagtat gccatgatcc 720
tggaattgt caacaacctg ctgctccatg tagaacctaa gcggaaggaa catagtgaga 780
agaagcaacg ggtcaggttc cagcttgaga tctctagcaa tccagaggag caacgcagca 840
gcatactgca tttgcaggag gctgtgcggc agcatgtggc ccaaatacga cagctggaga 900
agcagatgta ttctatcatg aagtctttgc aggatgacag caagaatgag aatctgcttg 960
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gtgaagaact gaatatcctc atcagggttt ttaaggattt ccaactgcag cgggctaaca 1080
agatggagct gcgaaagcac aagaagatgt gagtgtggtc cgtcgcactg agttttactt 1140
tgctcaggca cgggtggcgc tgacagagga agatggacag ctgggaattg ctgaattaga 1200
actgcagagg ttctcttaca gcaagggtgaa taagtctgat gacacagcag aacatcttct 1260
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gcggcccccag agctcctgcc agtctgggag acagctagct ctccgcctct tcagcaaagt 1380
tcggcccccct gttgggggta tctctgttaa ggagcatttt gaggtaaatg tgggtgcttc 1440
accatccagc tgacacacca ttcttccaca gatgatgggc ttttctttcc tggccgaagt 1500
tgga 1505
```

<210> 160

<211> 736

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (718)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (723)

<223> n equals a,t,g, or c

<400> 160

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aggcacgagg gacacttggg gtctggacgc aacggcggcg ggagcatgaa cgccttcca 60
gccttcgagt cgttcttgct cttcgagggc gagaagatca ccattaacaa ggacaccaag 120
gtacccaatg cctgtttatt caccatcaac aaagaagacc acacactggg aaacatcatt 180
aaatcacgtg cctgcttccc cttcgcttc tgccgtgatt gtcagtttcc tgaggcctcc 240
ccagccacgc ttctgttaca gcctgcagaa ctgtgagtca attaaacctc ttttcttcat 300
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aaattaccca gtttctcata gttctttata gcagtgtgaa aacagactaa tggacccttc 360  
tggttgaagg aatgcagcca ttctgcttgt ttgactatgt cctttctatt catctctatt 420  
tcctgggagg tgtttatcca agtgcaatag gaggtattgg tgaccgcaca gtcccctcag 480  
tgttctgcta gtaaatagtt gaaggttgat cattgatctt ctgcgttttc agtctggcat 540  
ggaaaagccc ctgtgcaact ggtaaagata tcaataagca cctggtgggt ggcgggggta 600  
gtccaggctt gtcttgcaac tgtatgttct cttcagaccc ctccctggcg atgccagatt 660  
cactgggctg gcagattctg cccccccaa aaaaaaaaaa aaaatattaa taataaanaa 720  
aanagactcc cagggga 736

<210> 161

<211> 995

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (59)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (889)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (899)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (928)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (933)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (938)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (974)

<223> n equals a,t,g, or c

<400> 161

gggtcgaccc acgcgtccgg gcggcctcgg cagcgggtgtt ctgcgccttg cgaasgggnc 60

tccggctcgg ctgcgggga ctgtgcacga ggttggcgac gcgccccgc gggccccaga 120  
tcaggccgca gagatcggga gccgcgggag cactaaggcg caagggccac agcagcagcc 180  
gggctcagag ggtcccagct atgccaaaaa agttgcgctc tggcttgctg ggctgcttg 240  
agctgggtgg actgtgagcg tcgtctatat ctttggaaac aaccgggtgg acgaaaatgg 300  
tgccaagatt cctgatgagt tcgacaatga tccaattctg gtacagcagt tgcgccggac 360  
atacaaatat ttcaaagatt atagacagat gatcatcgag cccaccagcc cttgccttct 420  
cccagaccct ctgcaggaac cgtactacca gccaccctac acgctcgttt tggagctcac 480  
cggcgtcctc ttgcatcctg agtggtcgct ggccactggc tggaggttta agaagcgccc 540  
aggcatcgag acctgttcc agcagcttgc ccctttatat gaaattgtca tctttacgtc 600  
agagactggc atgactgcgt ttccactcat tgatagtgtg gaccccatg gcttcatctc 660  
ctaccgccta ttcggggcgc ccacaagata catggatgga caccatgtaa aggatatttc 720  
atgtctgaat cgggaccag ctgcagtagt agttgtggac tgcaagaagg aagccttccg 780  
cctgcagccc tataacggcg ttgccctgcg gccctgggac ggcaactctg atgaccgggt 840  
cttgttgat ctgtctgcct tcctcaagac cattgcactg aatggtgtng gaggacgtng 900  
cgaaccgtgc tgggagcatt atgccctngg ganggatnga ccccgctggg cggcttttyc 960  
aaacagcggc aaancgggct tagaagcagg gagga 995

<210> 162

<211> 1125

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (972)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1023)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1077)

<223> n equals a,t,g, or c

<400> 162

gccctagtagt ggtccggaat tcccgggtcg acccagcgt ccgcccacgc gtccgcgctg 60  
gtgttgccgc gctggcgaca gtccgggttg cgagcggccc ggggcccggg cggccagggc 120  
cgctgcagga cgagaccctg ggtgtggcgt ccgtgccctc gcagtggagg gccgtccagg 180  
gcatccgcgg ggagacgaaa agttgccaga cggccagcat tgccactgcc agtgcacccg 240  
cccaggccag gaatcatgtg gacgcccagg tgcagacgga ggccccctg cctgtcagcg 300  
tgcagcccc gtcccagtay gacataacca ggctcgcagc ctttcttcgg agagtggagg 360  
ccatggtcat ccgagagctg aacaagaatt ggcaagacca cgcgtttgat ggcttcgagg 420  
tgaactggac cgagcagcag cagatgggtgt cttgtctgta taccctgggc taccgcagc 480  
cccaagcgca gggcttgcgt gtgaccagca tctcctggaa ctccactggc tctgtgttg 540  
cctgtgccta cggccggctg gaccatggg actggagcac gcttaagtcc ttcgtgtgtg 600  
cctggaacct ggaccggcga gacctgcgtc ccagcaacc gtcggccgtg gtggaggtcc 660  
ccagcgtgt cctgtgtctg gccttcacc ccacgcagcc ctcccagtc gcaggagggc 720  
tgtacagtgg tgaggtgttg gtgtgggacc tgagccgtct tgaggaccg ctgctgtggc 780



gcacaggcct gacggatgac acccacacag accctgtgtc ccagggtgtg tggctgccc 840  
agcctgggca cagccamcgg ttcaggtgc tkagtgtggc cacygacggg aaggtgctac 900  
tctggcargg catcggggta rgccagctgc agttcacaga rggcttcgcc tggttcatkc 960  
agcagctgcc anggagcacc aagctcaaga agcatccccg cgggagaccg aggtgggagc 1020  
canggcaggc tttcttcag tttgacctca ggttttcatt ttggcaggaa gcggttnccg 1080  
ttcaattttc ctggcattgg agagcagcct taagggtgc ccatt 1125

<210> 163

<211> 423

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (390)

<223> n equals a,t,g, or c

<400> 163

gggtcgaccc acgcgtccga gatggcggtt cgcagcaaga ggccggagca cggcgggccc 60  
ccggagctgt ttatgacaa gaatgaagcc cggaaatacg tgcgcaactc acggatgatt 120  
gatgtccaga ccaaattggc tggcgagct ttggagctcc tttgtctgcc ggaggtcagc 180  
cctgttacct cttgatatt ggctgtggt ctgggctgag tggagattat ctctcgatg 240  
aagggcacta ctgggtaggc atcgacatca gccctgccat gctggatgcg gccttgacc 300  
gagacactga gggagacctg cttctggggg acatgggcca gggcatcccc ttcaaaccag 360  
kttcattgat ggatgtatca gcattctgcn aatcagtggc tctgtaatgc aaaccaagaa 420  
gtc 423

<210> 164

<211> 1642

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1614)

<223> n equals a,t,g, or c

<400> 164

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gcctccccc ccaccacagc cccccaccca tcaagcttca gtcgggctgc tggacacccc 120  
tcggagccgt gagcgctcac catcccctct gcsgggcaac gtggtcccaa gcccactgcc 180  
cactcgccgg acgaggacct tctcggcgac ggtgcgggct tcacagggcc ccgtctacaa 240  
aggagtctgc aaatgcttct gccggtccaa gggccatggc ttcattaccc cagctgatgg 300  
cggccccgac atcttctctgc acatctctga tgtggaagg gagtatgtcc cagtggaagg 360  
cgacgaggtc acctataaaa tgtgtcccat cccacccaag aatgagaagc tgaggccgt 420  
ggaggtcgtc atcactcacc tggcaccagg caccaagcat gagacctggc ctggacatgt 480  
catcagctcc taggagatgg tggaaagcacc cctgtctctg tgcttgtggg agactttgcg 540  
gggaggaggc agcagacact ggagatgaca ttcttcaca cgagacggg cttcagccgg 600  
gcatggtccc tctcaagtat ctcttgagg aaggggtatg gggggcagg gtggggtgtg 660  
gggtgttccc ggccatcagc acagcctatg accattgcaa caacctctca ccatctgaag 720  
agcattaaaa gcatttaaaa aggaragggt cccactgggt gctgagtgga ggttccaacc 780

```
ccatcccagg gagtggatca aggggtggtat ttctccagct gctcagacac atgggctcaa 840
cccacagaat ccctcttcct cctggagctg gagggcccag attcccagat ctggccccct 900
ggcagcctga cagggacctt gcgtgacttc tccaaggcaa atttccacct aagtggccct 960
tgcgccctct ctggggcctg ggcaaagcag ttttctaatt ctgggcttgg ttggttctag 1020
gggagctggc ttgaagtggg kggggaaagg cgggggtggc ggtcttttga ttggacggat 1080
gttgcccttt ggtgcccttt cagtgggagg cgcatagct gcctgtcttg ggaagacagt 1140
tctcccagca ctcccacccc tgggcacagc aggctggtac tgggaggctg aaccctctt 1200
agagcctgac cttttcatct gccttctggt tgtgtgacca tcaactcaaca gccatttcac 1260
agccctgta attatggcgg cggggggctg ggggtggtgg ggtgggaagg gcttgtggag 1320
aggacacagt ctttgtttaa aaactttgtc ccgatccatc cagaaaagag taggtagctt 1380
gcacctgac agcctggcaa agtcaagaaa gttgaaggag aaacatacct ttggagaggg 1440
ggttttcttt aaaactagt ttaagaaatg cttagggatt tttttttct tatttttcat 1500
aactaaagct ttcaccaga gccggctctg ttgcacttt gctgccgaca ttgcaactt 1560
tttgcgaggg tgggagactg agtctcatc tgtcamccag gctggagtgc agtngcccga 1620
tctcagcttt actgcaacct ct 1642
```

<210> 165

<211> 1115

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (390)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (394)

<223> n equals a,t,g, or c

<400> 165

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aggaatgccg agtactgcag gggctcccca gggagtatgt gaatgccagg cactgtttgc 60
cgtgccaccc tgagtgtcag cccagaaatg gctcagtac ctgttttga ccggaggctg 120
accagtgtgt ggctgtgcc catcaagtgg atggcgctgg agtccattct ccgccggcgg 180
ttcaccacac agagtgatgt gtggagtatt ggtgtgactg tktgggagct gatgactttt 240
ggggccaaaac cttacgatgg gatcccagcc cgggaggatc cctgacctgc tggaaaaggg 300
ggagcggctg cccagccccc ccatctgcac cattgatgtc tacatgatca tggtaaatg 360
ttggatgatt gactctgaat gtcggccaan attncgggag ttggtgktg aattctccc 420
catggccagg gacccccagc gctttgtggt catccagaat gaggacttgg gccagccag 480
tcccttgac agcaccttct accgctcact gctggaggac gatgacatgg gggacctggt 540
ggatgctgag gagtatctg taccacagca gggcttcttc tgtccagacc ctgccccggg 600
cgctgggggc atggtccacc acaggcaccg cagctcatct accaggagtg gcggtgggga 660
cctgacacta gggtcggagc cykctgaaaag aggaggcccc caggtctcca ctggcaccct 720
ccgaagggct ggctccgatg tattttratg tgacctggga atgggggcag ccaaggggct 780
gcaaagcctc cccacacatg accccagccc tctacagcgg tacagtgagg accccacagt 840
accctgccc tctragactg atggctacgt tgccccctg acctgcagcc cccagcctga 900
atatgtgaac cagccagatg ttcggcccca gcccccttcg ccccgagagg gccctctgcc 960
tgctgcccga cctgctggtg ccactctgga aaggscgaag actctctccc cagggaagaa 1020
tggggtcgtc aaagagtttt tgcccttggg ggtgccgtgg agaacccca gtattgacac 1080
cccaggggag ggagcttgcc cttcagcccc acctt 1115
```

<210> 166  
<211> 1066  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (10)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (739)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (968)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1023)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1025)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1042)  
<223> n equals a,t,g, or c

<400> 166  
gggcacgagn cacctgagcc ccttgctctg caccggctcc caggagggca cctccatgga 60  
gggctccgcg cccgctgccc ctgccagagc caggcaccct caagaccagt ctggtggcta 120  
ctccaggcat tgacaagctg accgagaagt cccaggtgtc agaggatggc accttgcggt 180  
ccctggaacc tgagccccag cagagcttgg aggatggcag cccggctaag ggggagccca 240  
gccaggcatg gagggagcag cggcgaccgt ccacctcatc agccagtggg cagtggagcc 300  
caacgccaga gtgggtcctc tcctggaagt cgaagctgcc gctgcagacc atcatgaggc 360  
tgctgcaggt gctggttccg cagtggagaa gatctgcatc gacaagggcc tgacggatga 420  
gtctgagatc ctgcggttcc tgcagcatgg caccctgggt gggtgtgtgc ccgtgcccc 480  
ccccatcctc atccgcaagt accaggccaa ctcgggcact gccatgtggt tccgcacct 540  
catgtggggc gtcattctatc tgaggaatgt ggacccccct gtctggtacg acaccgacgt 600  
gaagctgttt gagatacagc ggggtgtgagg atgaagccga cgaggggctc agtctagggg 660  
aaggcagggc cttggtccct gaggcttccc ccatccacca ttctgagctt taaattacca 720  
cgatcagggc ctggaacang cagagtggcc ctgagtgtca tgccctagag acccctgtgg 780  
ccaggacaat gtgaactggc tcagatcccc ctcaaccctc aggtgggact cacaggagcc 840

ccatctctgg ggctatgccc caccagagac cactgcccc aacactcgga ctccctcttt 900  
aagacctggg ytcagtgtg gccctcagt gccaccact cctgtgtac ccagccccc 960  
gaggcagnaa rccaatgggt cactgttgcc cctaaaggg gggttttgaa ccaaggggga 1020  
aancnacggg gcctggttcc cntttgaaa gggttccct gggaaa 1066

<210> 167  
<211> 657  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (278)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (564)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (597)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (602)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (635)  
<223> n equals a,t,g, or c

<400> 167  
gtcgcgagcg ctgccgtcgg gaggcgctcc gaggttcgag gctgtgcccc gcgaccccg 60  
cttcggcgct cggtcgcag gatggatccc gtaccggga cagactcggc gccgctggct 120  
ggcctggcct ggctgcggc ctctgcaccc ccgccgggg gkttcagcg gatctcctgc 180  
accgtcgagg gggcaccgcc agctttggca agagcttcgc gcagaaatct ggctacttcc 240  
tgtgccttag ttctctgggc agcctagaga acccganga gaacgtggtg gccgatatcc 300  
agatcgtggt ggacaagagc cccctgccgc tgggcttctc ccccgctgc gamcccatgg 360  
attccaaggc ctctgtgtcc aagaagaaac gcatgtgtgt gaarctgttg cccctkggar 420  
ccamggacac ggctgtgttt gatgtccggc tgagtgggaa gaccaagaca gtgcctggat 480  
accttcgaat aggggacatg ggcggtttt ccatctggtg caagaaaggc caaggccccc 540  
aggccagttg cccaaagccc cgaagtccct agcccgggac atgcaagggc ttctctntgg 600  
angcagccag ccagcccaa gtaaggcg ggctncttgg aagccggaca agcgttc 657

<210> 168  
<211> 1026  
<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1011)

<223> n equals a,t,g, or c

<400> 168

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ggcacgagga gagatggagg ggcggcaggt gctggaggtc aagatgcagg tggagtacat 60
gtcattcagc gcacacgcgg acgccaaggg catcatgcag ctggtgggcc aggcagagcc 120
gkagagcgtg ctgctggtgc atggcgaggc caagaagatg gagttcctga agcagaagat 180
cgagcaggag ctccgggtca actgctacat gccggccaat ggcgagacgg tgacgctgcc 240
cacaagcccc agcatccccg taggcatctc gctggggctg ctgaagcggg agatggcgca 300
ggggctgctc cctgaggcca agaagcctcg gctcctgcac ggcaccctga tcatgaagga 360
cagcaacttc cggctggtgt cctcagagca agccctcaaa gagctgggtc tggctgagca 420
ccagctgcgc ttcacctgcc gcgtgcacct gcatgacaca cgcaaggagc aggagacggc 480
attgcgcgtc tacagccacc tcaagagcgt cctgaaggac cactgtgtgc agcacctccc 540
rgacggctct gtgactgtgg agtccgtcct cctccaggcc gccgccccct ctgaggaccc 600
aggcaccaag gtgctgctgg tctcctggac ctaccaggac gaggagctgg ggagcttctc 660
cacatctctg ctgaagaagg gcctccccca ggccccagc tgaggccggc aactcaccca 720
gccgccacct ctgccctctc ccagctggac agaccctggg cctgcacttc aggactgtgg 780
gtgccctggg tgaacagacc ctgcaggacc catccctggg gacagaggcc ttgtgtcacc 840
tgcctgcccc ggcagctgtt tgcaagttaa gaaacaaact ggtctccagg ctgtcttgcc 900
tttattcctg gttagggcag gtggtcctag acagcagttt ccagtaaaag ctgaacaaaa 960
aaaaaaaaaa aaaaaattgg gggggggccc gttaccatt tggcctttag nggggggttt 1020
aaatta                                           1026
```

<210> 169

<211> 774

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (730)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (733)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (754)

<223> n equals a,t,g, or c

<400> 169

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ggcataaaca tcgggtggtg ttcagatcct gctgccggca gctcgaggct aggatggctg 60
gagatgtgag ggcttttgct tcatacatc cgagcacagc tcagcaagat gctcttagct 120
agraaacaga ttttatgtgt taatgttaaa aattttgcag ttatttatct tgtggatatt 180
```

```
acagaagtgc ctgacttcaa caaaatgtat gagttatacg atccatgtac tgtcatgttt 240
ttcttcagga acaagcacat catgattgac ttggggactg gcaacaacaa caagattaac 300
tggggccatgg aggacaagca ggagatggtg gacatcatcg agacggtgta ccgcggggcc 360
cgcaaaargcc gcggcctggt ggtgtccccc aaggactact ccaccaagta ccgctactga 420
ggcgccctca gtctgcgcgg ataaatgtcg tggagccctt tttgtatgga aacgttttaa 480
gctattttaa gcctttggaa aatacaggaa gctccagggc tggagcacct ctgagatgga 540
attgataaca tggctttaac tcaccgaaat aaacaagcac gtggtgagag gagcaggcct 600
acttgtttgt tctcaggaaa cttaatgaat agattactga ttttcctagt caaagttaat 660
tcttaccctt ggagtaaaac gaaggtgttt atcctgtgag cctgtgcgtt ttgcatactg 720
ggttggtttn ctngggcttc ggtgacagca tatnccgcga gctgggcttt aaca 774
```

<210> 170

<211> 402

<212> DNA

<213> Homo sapiens

<400> 170

```
ggcacgagcg gcggtggggc ggacagccgg ggtgcgcact tgggcccccc tggccatggc 60
ggcgaagggtg gacctgagca cctccaccga ctggaaggag gcgaaatcct ttctgaaggg 120
cctgagtgcac aagcagcggg aggaacatta cttctgcaag gactttgtca ggctgaagaa 180
gatcccgaca tgggaaggaga tggcgaaagg ggtggctgtg aaggtggagg agcccaggta 240
taaaaaggac aagcagctca atgagaaaat ctccctgctc cgcagcgaca tcaccaagct 300
ggaggtggac gccatcgtca acgcccgaac cagctccccg cccccgagga gcctaattaa 360
agatcttcgt tgtggcaaaa aaaaaaaaaa aaaaaaaaaa aa 402
```

<210> 171

<211> 796

<212> DNA

<213> Homo sapiens

<400> 171

```
aggcatcggg gacagccgct gcggcagact cgagccagct caagcccga gctcgcaggg 60
agatccagct ccgtcctgcc tgcagcagcc caaccctgca caccaccat ggatgtyttc 120
aagaagggct tctccatcgc caaggagggc gtggtgggtg cgggtgaaaa gaccaagcag 180
ggggtgacgg aagcagctga gaagaccaag gagggggtca tgtatgtggg agccaagacc 240
aaggagaatg ttgtacagag cgtgacctca gtggccgaga agaccaagga gcaggccaac 300
gccgtgagcg aggtgtggt gagcagcgtc aacactgtgg ccaccaagac cgtggaggag 360
gcggagaaca tcgcggtcac ctccggggtg gtgcgcaagg aggacttgag gccatctgcc 420
ccccaacagg agggtagggc atccaaagag aaagaggaaag tggcagagga ggcccagagt 480
gggggagact agagggctac aggccagcgt ggatgacctg aagagcgctc ctctgccttg 540
gacaccatcc cctcctagca caaggagtgc ccgccttgag tgacatgcgg ctgcccacgc 600
tcctgccctc gtctccctgg ccacccttg cctgtccacc tgtgtgtgtg caccaacctc 660
actgccctcc ctgcgcccc cccaccctct ggtccttctg accccactta tgtgtgtgtg 720
aatttttttt ttaaattgatt ccaaataaaa cttgagccca ctyctaaaaa aaaaaaaaaa 780
aaaaaaaaag gggccc 796
```

<210> 172

<211> 478

<212> DNA

<213> Homo sapiens

<400> 172  
aattcggcag agcctgggtg cagggcagct aggggtctct gcattctcca catggtctca 60  
tgcccccttt tgtcccttac aggaggactt gaggccatct gcccccaac aggagggtga 120  
ggcatccaaa gagaaagagg aagtggcaga ggaggcccag agtgggggag actagagggc 180  
tacaggccag cgtggtatgac ctgaagagcg ctctcttgcc ttggacacca tcccctccta 240  
gcacaaggag tgcccgcctt gagtgcacatg cggtgcccc cgtctctgcc ctctctctcc 300  
tggccaccct tggcctgtcc acctgtgctg ctgcaccaac ctactgccc tcccctcgcc 360  
ccaccaccc tctggtcctt ctgacccac ttatgctgct gtgaattttt tttttaaatg 420  
attccaaata aaacttgagc ccactcctaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 478

<210> 173  
<211> 656  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (59)  
<223> n equals a,t,g, or c

<400> 173  
tttcccaatg cctgccacca cggagactca gggccacctg ccaccctccc tcgtgcctt 60  
ctgcccttgg gatggggcgc tcctgaatgt acgtgggccc cgggtgttac aaggaggtga 120  
tcattacaaa cctctgccag aagcaggtgg tggagaagat accactgccc ttttttgcca 180  
tgtccctgag cctgtccccc gggaccaccc tcctggctgt tggtttgtct gagtgcacgc 240  
tgaggctggt agactgtgcc atggggactg cccaagactt tgccggccac gacaacgcag 300  
tgcacctgtg caggtttaca ccktccgcca ggctgctctt cagggccgcc cgcaacgaga 360  
tccttgtgtg ggagggtccc ggctctgag atgcagcagg gactgtggtg gtgggcatca 420  
acgcctgtgc atgccaggca cctggacaca ggcttgccag aggcgccagg ttgtcaatgg 480  
cctcatgtcg ggacaggcca ggattcacgt aaatcgctg gagcaagctg ttgtaaat 540  
ggcgccctgt gaatactttc atacctgttg cctttttgcc taagaaatct ttaatgtttc 600  
tatcttgtaa taaacatggg catttattgc aaaaaaaaaa aaaaaaaaaa aaaaaa 656

<210> 174  
<211> 1891  
<212> DNA  
<213> Homo sapiens

<400> 174  
gagccccctc cgagagggga gaccagcggg ccatgacaag ctccaggctt tggttttcgc 60  
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<213> Homo sapiens

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&lt;210&gt; 176

&lt;211&gt; 2411

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 176

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<213> Homo sapiens

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<222> (1276)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (1289)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (1326)

<223> n equals a,t,g, or c

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&lt;210&gt; 178

&lt;211&gt; 1614

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1213)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 178

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<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

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<221> misc feature

<222> (4288)

<223> n equals a,t,g, or c

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tgcattttgt accagtggaa ctttttatac tggagattaa aaaaaaaatg gaaatttttg 3780  
tggcttgctc tgggtggccc ctgacaatga ctgatttcaa gtttgatttc gggttgattg 3840  
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aacagtcaaa cttatttttg taatgtatgt tattgtgtga tgcagttttt tgcttctgtc 4200  
tccaatatta aaccattttc ctaataaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4260  
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&lt;210&gt; 180

&lt;211&gt; 243

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
<221> misc feature  
<222> (235)  
<223> n equals a,t,g, or c

<400> 180  
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cagctcctcr cgccatcacc atcgccgccc ccggttccac ctrccccaac agcccctgct 120  
ccagagggaa gtgtgggtgtg tgggcacaac gggaaacgct aaccaggcac agagctcaac 180  
ggagcagaca ctgctgaagc ccaagtgaga aaccacggcg ctttggcgtg taacntggaa 240  
tat 243

<210> 181  
<211> 813  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (266)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (723)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (726)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (738)  
<223> n equals a,t,g, or c

<400> 181  
aattcggcag agaccaggtg tacctgagct acaataacgt ctccctcttg aagatgcttg 60  
tggccaagga caactgggtg ctgtcctcgg agatcagtca ggtccgcctg tacactctgg 120  
aggatgacaa gttcctctcc ttccacatgg agatggtggt gcatgtggat gcagmccagg 180  
ccttcctgct gctctcggac ctgmgtcaga ggccagagtg ggacaagcac taccggagcg 240  
tggagctagt gcagcaggta gacranggac gacgccatct accacgtcac cagmccctgmc 300  
ctcggaggtc acacaaagcc ccaggacttc gtgatcctgg cctcgaggcg gaagccttgt 360  
gacaatgggg acccctatgt catcgcgctg aggtcgggtc cgctgcccac acaccgagag 420  
acgccagagt acagacgcgg agagaccctc tgctcaggct tctgcctctg gcgcgagggg 480  
gaccagctga ccaaggtagc ctgtagtaga ctcggtcctt gtccacagcc cttagctgcca 540  
gcaatgctgt cctcacagag gcatagtcgc ccccagctgg gttgtgctcc actgtgacgg 600  
tggcccgggg ggaggatgcc agcagcctgc ctatggytgc cagctgtgct gtgagcccag 660  
cagcatggcc tgcatctggg aaggagacaca ggttgctccag agcccctggc acaactgctg 720  
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gggccagcct ggtggccaca gtgcacgtgg ggg

813

&lt;210&gt; 182

&lt;211&gt; 822

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (37)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (49)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (370)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (567)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 182

ggttttacat gaccgcagtc gccctcagtt tcaccngta ggaatcggn c tggggatgca 60  
ccgtgctact ctcttcctcc aggccggtcc ccggcgcggtg cgcgcgatcc atgtccatgt 120  
ccgcgcctat caataaagtt gctcacttgt tgccggcccg ctagmccgaa aggttgcgcg 180  
cgcagmccga gaagtctcgc gatagccagc cgcggctgcc cttgcgcttc ccgagctggc 240  
gggggtccgtg gtgcgggatc gagattgcgg gctatggcgc cgaagttttt cgtcagtact 300  
gggatatccc cgatggcacc gattgccacc gcaaagccta cagcaccacc agtattgcca 360  
gcgtcgctgn cctgaccgcc gctgcctaca ggtcacact caatcctccg ggcaccttcc 420  
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ttggcctcac cacctgcac agcgcccatg tccgcgagaa gcccgacgac cccctgaact 540  
acttcctcgg tggctgcgcc ggaggcntga ctctgggagc acgcacgcac aactacggga 600  
ttggcgccgc cgcctgcgtg tactttggca tagcggcctc cctggtcaag atgggccggc 660  
tggagggtg ggaggtgttt gcaaaaccca aggtgtgagc cctgtgcctg ccgggacctc 720  
cagcctgcag aatgcgtcca gaaataaatt ctgtgtctgt gtgtgaaaaa aaaaaaaaaa 780  
aaaaaaaaat yggggggggg cccskaacca attkccctta ag 822

&lt;210&gt; 183

&lt;211&gt; 1095

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1082)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1094)

<223> n equals a,t,g, or c

<400> 183

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gccagttcca gcccgacccc cgcgtcgggtg cccgcgcccc tccccggggc ccgccatggg 120
cctcacccgtg tccgcgctct tttcgcggat cttcggaag aagcagatgc ggattctcat 180
ggtttgcttg gatgcgctg gcaagaccac aatcctgtac aaactgaagt tgggggagat 240
tgtcaccacc atcccaacca taggcttcaa tgtagaaca gtggaatata agaacatctg 300
tttcacagtc tgggacgtgg gaggccagga caagattcgg cctctgtggc ggcactactt 360
ccagaacact cagggcctca tctttgtggt ggacagtaat gaccgggagc ggggtccaaga 420
atctgctgat gaactccaga agatgctgca ggaggacgag ctgcgggatg cagtgtgct 480
ggtatttgcc aacaagcagg acatgcccac cgccatgccc gtgagcgagc tgactgacaa 540
gctggggcta cagcacttac gcagccgcac gtggtatgtc caggccacct gtgccaccca 600
aggcacaggt ctgtacgatg gtctggactg gctgtcccac gagctgtcaa agcgctaacc 660
agccaggggc agggccctga tgcccgaag ctctgcgtg catccccggg atgaccagac 720
tcccggaact ctcaggcagt gccctttcct cccacttttc ctccccata gccacaggcc 780
tctgctcctg ctctgcctg catgttctct ctggtgttg agcctggagc cttgctctct 840
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ggccccctct tccagaggag gaggaggat ctgggtttcc ttttttttt ctgttttggg 960
tgtactctag gggccaggtt gggaggggga aggtgagggc ttcgggtggt gctataatgt 1020
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ngggggggcc ccgna 1095
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<210> 184

<211> 3675

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2204)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3329)

<223> n equals a,t,g, or c

<400> 184

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tcgtgtctaa tggaaacccc ctgtgcatg cacagctccg gcagctccca gcgatgacgg 120
ccctgcagac cctgcacctg cggagaccca gcgcacccag agcaacctgc ccaccagcct 180
ggagggcttg agcaacctcg cagacgtgga tctgtcctgc aatgacctga cagggtgccc 240
cgagtgtctg tacacctcc ccagcctgcg ccgcctcaac ctacagcagc accagatcac 300
ggagctgtcc ctgtgcatag accagtgggt gcacgtgga actctgaacc tgtcccgaaa 360
tcagctcacc tcaactgcct cagccatttg caagctgagc aagctgaaga agctgtacct 420
```



gaattccaac aagctggact ttgacgggct gccctcaggc attggcaagc tcaccaacct 480  
 ggaagagttc atggctgcca acaacaacct ggagctggtc cctgaaagtc tctgcaggtg 540  
 cccaaagctg aggaacttg tcctgaacaa gaaccacctg gtgaccttc cagaagccat 600  
 ccatttcctg acggagatcg aggtcctgga tgtgcgggag aacccaacc tggcatgcc 660  
 gcccaagccc gcagaccgtg ccgctgagtg gtacaacatc gacttctcgc tgcagaacca 720  
 gctgcggcta gcgggtgcct ctctgctac cgtggctgca gctgcagctg cgggagtg 780  
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cacgtgtgaa gccccctcac tcttccgcta gggataaagc agatgtggat gccctttaag 3600
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<210> 185

<211> 1040

<212> DNA

<213> Homo sapiens

<400> 185

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caggagccat gcagctgtgc tgggtgatcc tgggcttcct cctgttccga ggccacaact 120
cccagcccac aatgacccag acctctagct ctccaggagg ccttgccggt ctaagtctga 180
ccacagagcc agtttcttcc aaccaggat acatcccttc ctccaggagt aacaggccaa 240
gccatctrtc cagcactggt accccaggcg cagggtgtcc cagcagtgga agagacggag 300
gcacaagcag agacacattt caaactgttc ccccaattc aaccaccatg agcctgagca 360
tgagggaaga tgcgaccatc ctgccagcc ccacgtcaga gactgtgctc actgtggctg 420
catttggtgt tatcagcttc attgtcatcc tgggtggtgt ggtgatcatc ctagttggtg 480
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ggagtccagg gctgtctgaa agctgtctca cagccaatgg agagaaagac agcatcacc 600
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acaaggagga agagatggaa ttagtagagg caatgaacca catgtaaat attttattgt 780
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cacctcctca gagccacagg aaagaggagg tgacagagag agagcaagga aagtgatgag 960
gtggattgat actttctact ttgcatataa attattttct agcctgcaaa aaaaaaaaaa 1020
aaaaaaaaaa aaaaactcga 1040
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<210> 186

<211> 817

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (76)  
<223> n equals a,t,g, or c

<400> 186

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acccacgcgt ccgcangagc ggccgggtgg cgggaggaac cgttacggga actgaagttg 120
cggattaagc ctgatcaaga tgacaacctc ccaaaagcac cgagacttcg tggcagagcc 180
catgggggag aagccagtgg ggagcctggc tgggattggg gaagtcctgg gcaagaagct 240
ggaggaaaag ggttttgaca aggcctatgt tgccttggc cagtttctgg tgctaaagaa 300
agatgaagac ctcttccggg aatggctgaa agacacttgt ggcgccaacg ccaagcagtc 360
ccgggactgc ttcggatgcc ttcgagagt gtgcgacgcc ttcttgtgat gctctctggg 420
aagctctcaa tccccagccc tcattccagag ttgcagccg agtagggact cctccccctgt 480
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tgggagtttt ctccccaac catttcaact tttttttgga ttctcgctct tgcatgcctc 600
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cccgcccca tccctcacc ccaccctcac ttccaatccg ttgtatacca ttggtctcct 720
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tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 817
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<210> 187

<211> 1080

<212> DNA

<213> Homo sapiens

<400> 187

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cgacctgaac gcaaaagtccc tgatggacga gacgcccctt gatgtgtgcg gggacgagga 180
ggtgcggggc aagctgctgg agctgaagca caagcacgac gccctcctgc gcgcccagag 240
ccgccagcgc tccttgctgc gccgcgcgac ctccagcgcc ggcagccgcr ggaagggtgt 300
gaggcggttg agcctaacc agcgcaccga cctgtaccgc aagcagcacg cccaggaggc 360
catcgtgtgg caacagccgc cgcccaccag cccggagccg cccgaggaca acgatgaccg 420
ccagacaggc gcagagctca ggccgcccgc cccggargag gacaaccccg aagtggtcag 480
gccgcacaat ggccgagtag ggggtcctcc agtgcggcat ctatactcca agcgactaga 540
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<210> 188

<211> 1286

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature  
<222> (1245)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1254)  
<223> n equals a,t,g, or c

<400> 188  
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actgaattat tcaactgcat atgactctaa acaccaaata cgtaatgcct ctaatgtaaa 120  
gcaccatgac tctagtgtc ttggtgtata ttcttacata ccttttagtg aaaatcctta 180  
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ttattacaat tcacatgatt ctttatcact gaattctcca accaatattt cctcactatt 360  
gaaccaggag tcagctgtac tagcaactgc tccaaggata gatgatgaaa tccccctcc 420  
acttctgtg cggacacctg aatcatttat tgtggttgag gaagctggag aattctcacc 480  
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gggtggaaca tctgaaccaa agaaatttga tgactctgtg atacttagac caagcaagag 600  
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acagacactg aagactcctg gaaaaagttt cacaaggagt aagagtttga aaattttgcg 840  
aaacatgaaa aagartatct gtaattcttg cccaccaaac aagcctgcag aatctgttca 900  
gtcaataaac tccagctcat ttctgaattt tggttttgca aaccgtttt caaaaccaa 960  
aggrccaagg aatccaccac caacttgga tatttaataa aactccagat ttataataat 1020  
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agcaaaatgc caataagtg cagttttgca tttcatatc atttgcatg agttgaaaac 1200  
tgcaataaaa agtttgtcac ttgagcttat gtacagaatg ctatntgggg aacncttcta 1260  
ggatgggttt tatttttcca tttttg 1286

<210> 189  
<211> 1738  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1480)  
<223> n equals a,t,g, or c

<400> 189  
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gtcgtggccc ccattggtga ccagagcgag ctggcctgga ggctgctgag ccggcgccac 180  
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taccggaagg agaacctgta ctgcgaggtg tgccccgagg accggcccct catcgtgcag 300  
ttctgtgcca atgaccgga ggtgtttgtt caggcggctc tcctggctca ggattactgt 360  
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ggcctggaaa tgctgcagtg gggagcaggc cccaggctgg acctgcctg tcctcagcac 1680  
gcgtgtgcaa aagtgaacaa taaatcatth caaagatgaa aaaamaaaaa aaaaaaaa 1738

<210> 190

<211> 1923

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1829)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1875)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1910)

<223> n equals a,t,g, or c

<400> 190

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atgaccgctt ccacgagatg cagctggctc tggcccagaa ggaccaggag atcgcttcc 180  
tgcgctccat gctgggaaag ctctcggaga agatcgacca gctagagaag agcctggagc 240  
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ggcgggacgc atccatgtta aatgacgagc tgtccacat caacgcgcgg ctgaacatgg 360  
gcatcctagg ctctacgac cctcagcaga tcttcaagt caaagggacc tttgtgggcc 420

accagggccc tgtgtggtgt ctctgcgtct actccatggg tgacctgctc ttcagtggct 480  
cctctgacaa gaccatcaag gtgtgggaca catgtaccac ctacaagtgt cagaagacac 540  
tggagggcca tgatggcatc gtgtctggctc tctgcatcca ggggtgcaaa ctctacagcg 600  
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ccgtggctgc ctgtacatg ccctgcttnc acgtggctgc acgtgacac acccacattc 1860  
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agc 1923

<210> 191

<211> 250

<212> DNA

<213> Homo sapiens

<400> 191

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tcagtgtctt tacatttgtt ttttctttta tgctagtgtg aaatggagga tgaarataca 180  
attgrtgtgt tccaacagca gacgggrggt gtctactgaa aagggaacct gcttctttac 240  
tccagaactc 250

<210> 192

<211> 1902

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (8)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (19)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (763)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1898)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1900)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1901)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1902)  
<223> n equals a,t,g, or c

<400> 192  
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c c a a a a a t c a a a g g a g g t g c g g a t g t t t c a g g g g t g t c a g t g c c c c a r a c a t c a g c c t t 120  
g g t g a a g g g c a t t t r a g t g t t a a a g g t t c c g g g g t g a g t g g a a g g g a c c c c a a g t c t c c 180  
t c t g c t c t c a a c t t g g a c a c a t c t a a g t t t g c t g g g g g c c t t c a t t t c t c a g g a c c a a a g 240  
g t g g a a g g a g g t g t g t g a a a g g a g g t c a g a t t g g a c t c c a g g c t c c t g g g c t g a g t g t g t c t 300  
g g g c c t c a a g g t c a c t t g g a a g t g g a t c t g g a a a a g t a a c a t t c c c t a a a a t g a a g a t c 360  
c c c a a a t t t a c c t t c t c t g g c c g t g a g c t g g t t g g c a g a g a a t g g g g g t g g a t g t t c a c 420  
t t c c c t a a a g c a g a g g c c a g c a t c c a a g c t g g t g c t g g a g a c g g c g a g t g g a a g a g t c t 480  
g a a g t c a a a c t g a a a a g t c c a a g a t c a a a t g c c c a a g t t t a a t t t t t c c a a a c c t a a a 540  
g g g a a a g g t g g t g t c a c t g g c t c a c c a g a a g c a t c a a t t t c t g g g t c c a a a g g t g a c c t g 600  
a a a a g t t c a a a g g c c a g c c t g g g c t c t c t g g a a g g a g a g g c a g a g g c c g a a g c c t c t t c a 660  
c c g a a a g g c a a a t t c t c c t t a t t t a a a a g t a a g a a g c c a c g g c a c c g c t g c a a a t t c a t t 720  
c a g t g a t g a a a g a g a g t t c t c t g g a c c t t c c a c c c c g a c g g g n a c g c t g g a g t t t g a a g g 780  
t g g g g a a g t g t c t c t g g a a g g t g g g g a a a g t t a a g g g a a a c a c g g g a a g c t g a a a t t c g g 840  
t a c c t t t g g t g g a t t g g g g t c a a a g a g c a a a g g t c a t t a t g a g g t g a c t g g a g c g a t g a 900  
t g a g a c a g g c a a g t t a c a g g g a g t g g g g t g t c c c t g g c c t c t a a g a a g t c c c g a c t g t c 960  
c t c c t c t c t a g c a a t g a c a g t g g g a a t a a g g t t g g c a t c c a g c t t c c c g a g g t g g a g c t 1020

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ctgcctcagc aatcatgcaa agaccttgcc tggcccgtg gcaagcgtg aaaaaccgac 1200
cgctgttagg ctccctggaac tatacagata ggtaaagagt tccaagttcg tccagcccat 1260
gtgcaaagtc aacagtattt gccttaagat ttcatatata tatatttttt tgcattgact 1320
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ccgccatgtt cctgatatta gttctgattt ctttttaaca aatgttatca tgattaagaa 1800
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gcaataaag ckgttattaa cctgaaaaaa aaaaaanan nn 1902
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<210> 193

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (528)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (535)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (559)

<223> n equals a,t,g, or c

<400> 193

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gagactggat ctgttcaaac agcaaacgcc cacagatggc ccagaggtgg tggtagtcag 180
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cagccagttt ggtgctgacg gtgagaggaa attagaatct gtttgcaaat tgtccaaccc 300
acccctcaa catgaggggc ttccattttc tgtgttttgt aagggaactg tttccttcat 360
gccgccatgt tcctgatatt agttctgatt tctttttaac aaatgttatc atgattaaga 420
aaatttcag cactttaatg gccaat AAC tgagaatgta agaaaattga tgctgtacaa 480
ggcaataaaa gctgtttatt aaccttgaaa aaaaaaaaa aaagggngg cccgnccat 540
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tgccctaggg ggggttaant

560

&lt;210&gt; 194

&lt;211&gt; 590

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (589)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (590)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 194

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tgccgggtgc tgaaccggtg tggcgaggcg gcgcggagcc tgcccctggg cgccaggtgt 120  
ttcgggggtgc ggggtctcgc gaccggggag aagggtcacgc acactggcca ggtttatgat 180  
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gatggcggcg ggggagctct tggccaccca aaagtgtata taaacttggg caaagaaaca 360  
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aagctcgtcg gttctgtgcg aagggtattc ctggtgctga ataaagggtg ttgctgtcaa 540  
gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaann 590

&lt;210&gt; 195

&lt;211&gt; 691

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (10)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (579)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (618)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

<222> (639)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (657)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (672)  
<223> n equals a,t,g, or c

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agatgagata aaactcatgt gaatatcagt tttaaggctg gtgggttcatt tgttttgggc 180  
atattgagtc aggattgact aatgaactgt agaggttttg cattatgcaa atgctcttaa 240  
tttcttgat taggaattag acgctcccc ccaagtctta aataatgttt taatctgtat 300  
ccttttatta taagaagatt agtaatatc tacagataat aacaacaact ggtatagtat 360  
attttattta cattcttcac tcttaggaga aaatgctgag aagcttctgc agttcaagcg 420  
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gccatttagg anccaaaaat tttgggtttt g 691

<210> 196  
<211> 1772  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (2)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1749)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1769)  
<223> n equals a,t,g, or c

<400> 196  
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ttttgcaact ctartgtctc actttttaaag gaacagcttg attgcaaagg agaaaaataga 240  
taagcaatga akttatctcc aacttcctaa aggcttatga cttctaaaaa gtgaatctat 300  
cagcattcca catcagattt aaagcatcaa atgcctgtga aacagcaaag atggttgaag 360  
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aaaatgatgg atataagtgg tagctgtatc tagtgaagtg tctgtcagta agtgaaacat 840  
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cttttgtctg attgttttat aagcctactt tacctcccag tcttgaaaac aagttttagt 1020  
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gttgttggat tagaggaact aacccaactt atatgatttt ttttttgttt ttgtcgtgta 1140  
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cgcytctgtg aggaccttct ggctcttgag ataccctaaa tatttaagat atttagatat 1380  
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atgaccagat acctgtttga tagtttactg acctagcaga tgtgtggaag aggaatcaga 1500  
tcttgattct tctgggttta tactggttgt aaaacagaat gatacagaaa atgttttcct 1560  
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1740  
aaaaaagana aaaaaaaaaa ggggggcnc cc 1772

<210> 197

<211> 675

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (657)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (671)

<223> n equals a,t,g, or c

<400> 197

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gtggagtctt tgtccacgtc cattgtctag ctcaaagtgg tacagaccaa gtatgtggaa 180  
gccaaaggact gtctgaacgt gctgaacaag agcaacgagg ggaagaatt actcgtccca 240  
ctgacgagtt ctatgtatgt ccttgggaag ctgcatgatg tggaaacacgt gctcatcgat 300  
gtgggaactg ggtactatgt agagaagaca gctgaggatg ccaaggactt cttcaagagg 360  
aagatagatt ttctaacc aa gcagatggag aaaatccaac cagctcttca ggagaagcac 420

gccatgaaac aggccgtcat ggaaatgatg agtcagaaga ttcagcagct cacagccctg 480  
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ccctttgggc gtggcttcct ggtgatggga aggtcttctg gttttaatgc caataaatgt 600  
gccagctggg caraaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaccccnngg 660  
gggggcccgg naccc 675

<210> 198

<211> 557

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (451)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (461)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (464)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (488)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (492)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (495)

<223> n equals a,t,g, or c

<400> 198

tttaggtgac acgtatagaa ggtcgctgc aggtaccggw ccggaattcc gggtcgaccc 60  
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gccccgcgcg tcgtgaagaa gcaggaggcc aagaaggctg tcaaccgcct gttcgagaag 180  
cggcccaaga acttcggcat cggctcagc cggcacgcgc gatcctctac aagcggctga 240  
gtcaagtggc cgcgtacat ccggctgcag cggcacgcgc gatcctctac aagcggctga 300  
aggtgcccgc cgccatcaac cagttcacgc aggcgctgga ccgccagacg gccacgcagc 360  
ttgcttgaag ctggcgaca attaccggcc cgagacgaag caggagaaga agcagcgggt 420  
gttgccccgc gcggagaaga aarcggcccg ncaaggggga ntnccgaac aagcggsgcc 480  
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gccattgggtt cgttatt

557

&lt;210&gt; 199

&lt;211&gt; 2611

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2549)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2560)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2585)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 199

tcnccgggtcg acccacgcgt ccggcgagga gtaccttacc aacttggtccc acatggacat 60  
cgacaaggac tggaggcccc gctgtacctc acccccaggg gctgggtccct ctccctccag 120  
cgctactacc aagtgtgtcca cgaaggggca gaactcaggc acctcgacac tcagggtccag 180  
cgctgtgagg acatcctgca gcagctgcag gccgtgttac cccagataga catggaaggg 240  
gatcgcaaca tctggatcgt gaagccagga gccaaagccc gcggacgagg catcatgtgc 300  
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gacagctata tccgcttttc cacgcagccc ttctccctga agaacctgga caactcagtg 540  
cacctgtgca acaactccat ccagaagcac ctggagaact catgccatcg gcatccactg 600  
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gacttcgtgt tcggggagga cttccagccc tggtgtattg agatcaacgc cagccccacg 840  
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tataagcagc ctgctgtgga ggtgcctcaa tatgtgggca tccggctcct ggtagagggc 1020  
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ctctgtgac ccagcgaggc tctggggaag gcaaggactc ggggaccctt acccacaggt 1140  
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gggccaggtc ctcagacgac agcacagcaa gctggtgggc actaaggccc tgtcgaccac 1440
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tytgcagaag gcatkggtct atcccttctt cagcaaaggg gcaaggtcac taaaaatgaa 2520
catccataag ccacaaccac tggagaaant tttgcactgn ttagtgtagt tggttgaatg 2580
tggnccccg gaaagagatg ttacttgac c 2611
```

<210> 200

<211> 2316

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2280)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2282)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2302)

<223> n equals a,t,g, or c

<400> 200

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gtgggtccag gtggggctgc tggccgtgcc cctgcttgct gcgtacctgc acatcccacc 120
ccctcagctc tccccgtccc ttactcatg gaagtcttca ggcaagtttt tcacttacia 180
gggactgcgt atcttctacc aagactctgt ggggtgtggtt ggaagtccag agatagtgtg 240
gcttttacac ggttttccaa catccagcta cgactggtac aagatttggg aaggctctgac 300
cttgagggtt catcggttga ttgcccttga tttcttaggc tttggcttca gtgacaaacc 360
gagaccacat cactattcca tatttgagca ggccagcatc gtggaagcgc ttttgcgga 420
tctggggctc cagaaccgca ggatcaacct tctttctcat gactatggag atattgttg 480
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```

tcaggagctt ctctacaggt acaagcagaa tcgatctggt cggcttacca taaagagtct 540
ctgtctgtca aatggaggta tctttctga gactcaccgt ccactccttc tccaaaagct 600
actcaaagat ggaggtgtgc tgtcaccat cctcacacga ctgatgaact tctttgtatt 660
ctctcgaggt ctaccccag tctttgggcc gtatactcgg ccctctgaga gtgagctgtg 720
ggacatgtgg gcagggatcc gcaacaatga cgggaactta gtcattgaca gtctcttaca 780
gtacatcaat cagaggaaga agttcagaag gcgctgggtg ggagctcttg cctctgtaac 840
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tgttgtgtag tcaagtcacc atgctgaatg tacactgatt cctttatgat gactgcttaa 1980
ctccccactg cctgtcccag agaggctttc caatgtagct cagtaattcc tgttacttta 2040
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gctgaatact ttttttttaa agccacattt cattgtctta gtcaaagcag gattattaag 2160
tgattattta aaattcgttt ttttaaatga gcaacttcaa gtataacaac tttgaaactg 2220
gaataagtgt ttattttcta ttaataaaaa tgaattgtga caaaaaaaaa aaaagggccn 2280
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```

<210> 201

<211> 1147

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (11)

<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (12)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (19)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1145)  
<223> n equals a,t,g, or c

<400> 201  
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aaggtacagt cgccgcgtgc ggagcttggt actggttact tggcctcatg gcggtccgag 120  
cttcgttcga gaacaactgt gagatcggct gctttgccaa gctcaccaac acctactgtc 180  
tggtagcgat cggaggtctca gagaacttct acagtgtgtt cgagggcgag ctctccgata 240  
ccatccccgt ggtgcacgcg tctatcgccg gctgccgcat catcgggcgc atgtgtgttg 300  
ggaacaggca cggctctcctg gtacccaaca ataccaccga ccaggagctg caacacattc 360  
gcaacagcct cccagacaca gtgcagatta ggcgggtgga ggagcggctc tcagccttgg 420  
gcaatgtcac cacctgcaat gactacgtgg ccttggtcca cccagacttg gacagggaga 480  
cagaagaaat tctggcagat gtgctcaagg tggaaagtctt cagacagaca gtggccgacc 540  
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cttcaattga agaccaggat gagctgtcct ctcttcttca agtccccctt gtggcgggga 660  
ctgtgaaccg aggcagtga ggtgattgctg ctgggatggt ggtgaatgac tgggtgtgct 720  
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cctgagtcac cttccaagtt gttccatggg ctcttggtc tggactgttg ccaaccttct 900  
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gctgtcctgt gccaccccat taaagtgcag ttccctccgg aaaaaaaaaa aaaaaaaggg 1140  
cggcnac 1147

<210> 202  
<211> 688  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (477)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (684)



<223> n equals a,t,g, or c

<400> 202

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acgtaccggt ccggtaatc ccgggtcgac ccacgcgtcc gtcggcgagg cgctgttgag 60
ggagtcgggc cgcgactgtg gtcgttttta taccttcccg cgcggacgcc ggcgctgcca 120
acggaagggc gggtaggacg gagtttcgtc atgttgcca ggcccatttg agatctttga 180
agatatcttc aacgtgaggc tctgctgcca tgaaggtgaa gattaagtgc tggaaaggcg 240
tgggcacttg gctctgggtg gccaacgatg agaactgtgg catctgcagg atggcattta 300
acggatgctg ccctgactgc aaggtgcccg gcgacgactg cccgctggtg tggggccagt 360
gctcccactg cttccacatg cattgcatcc tcaagtggct gcacgcacag caggtgcagc 420
agcactgccc catgtgccgc caggaatgga agttcaagga gtgaggcccg acctggntct 480
cgctggaggg gcacctctgag actccttctc catgctggcg ccgatggctg ctggggacag 540
cgccccctgag ctgcaacaag gtggaaacaa gggctggagc tgcgtttgtt ttgccatcac 600
tatgttgaca cttttatcca ataagtgaat actcattaaa ctactcaaat cttaaaaaaa 660
aaawaaawaa atctcggggg gggncccc 688
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<210> 203

<211> 304

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (269)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (287)

<223> n equals a,t,g, or c

<400> 203

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aaatgtgaaa actaaggcct tgcaagccta tggttcaccc aggggtagga tcaggcacct 60
taactctaga gcccattctc ctaaccactg agccatgatt gtcttacaat tttgaatact 120
gcaaaactgg aagaattgtc tggctattat ctaagctgtt cataagctgg aacaagtaga 180
tctgagggta agaggagttc tgttttaact aggactgagt ttcaaataga gatgtttcag 240
actatagagg gggaaaaaatg gcckgggang tccataaatc taagccngtt tcatggatgt 300
tttt 304
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<210> 204

<211> 417

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (380)

<223> n equals a,t,g, or c

<400> 204

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gggtcgaccc acgcgtccgc gcgggagggg acggagctcg gcgtgcttgc tgctggaggg 60
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tgatggccct gcaaggctgt gggctccgac ctcaccggga gtcgamarcg agaggttcgc 120  
cgaagagcga ggttctgggc gagcgctgaa cgccggcccc aagcaccg ggtctttaca 180  
cagtcgcgct ccacagactc tgacgaagac gtggatctgc tctcgcttta gctgctcgcg 240  
gtcctccaga tcatgtccgc gactcctgcg actccgcgcg gaaaaaaaaaag tttgccaggc 300  
gtggactcaa tgacytttcc aastgtgcgc ctgcytgccct ggaccgggtt gagcgcggtt 360  
gcccaagttg aactttttgn ggggaggggt ttctctaagg gctgttgtct caatggg 417

<210> 205

<211> 551

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (450)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (458)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (471)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (484)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (519)

<223> n equals a,t,g, or c

<400> 205

gggtcgaccc acgcgtccga ctagttctag atcgcgagcg gcccgccctt tttttttttt 60  
tttttttttt tggtttccag agtttggtt tattttgcag tacagaaatc atctggagcc 120  
gtctgagaca gacatccctg aagcggaggc tctgtcaaata caatactgcg tcgcacttrg 180  
tccgttgagg aagccacacc tgggttaciaa aagaagcttc tacgtttacc cgctgtacca 240  
cggatttctt tcccctttgc tcttaccat tttaccaggt gaaaacaccg cacagaggct 300  
tccctcggaa tgacgctcgg gtctggagtt gggttagaat tgtggggcccg cgtgaccccc 360  
acctgtggct gtgttccgtg gccctgtcct aaacagctga cgggacacag acgtagaggg 420  
gcggggccac gcagggatgc tgttcccaan tcacgganta tctggtgggc ntcgcaatgg 480  
ccantgggac agatggcacg tgaaaggggc cgttccggnt ctcaagcggc agaagcacia 540  
gaccgcggag g 551

<210> 206

<211> 1101

<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (21)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (479)  
<223> n equals a,t,g, or c

<400> 206  
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ggcgccctgaa cccaagacct ctggatgagc tgccccgttc agaccatgga tcctgaggtg 180  
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agccccgcgc atgaccgtcg cccactgccca ggtggggacg aggccatcac tgccatctgg 300  
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ggtgccaccg actgggggtga cagcagggcc tatctggcgg acccactggg ggtgggctgct 540  
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gcccctgggc tgggtggacgt acctgggtgg caccctgagc ctcaggccct gtgccctggg 660  
ggcagccccc agcaccagga cctcgtggg cagctggtgg tacatgaact cttttccagt 720  
gtccttcagg agatctgtga tgaggtgaac ctgccgctgc tcaccctgag ccagcccctg 780  
ctgttkggca tcgcccga aa tgagaccagt gctggccgag ccagtgccga gttctatgtc 840  
cagtgcagcc tgacttctga gcagggtgagg aagcactacc tgagtggggg acccgaggcc 900  
cacgagtcta caggaatctt ctttgtggag acacagaacg tgcggagatt gcccagagacg 960  
gagatgtggg ctgaactctg cccctcgcca aaggcgccat catcctctac aaccgggttc 1020  
aggggaagtcc cactggagcg gccctagggt cccagccct actcccgccg ctctgaaaat 1080  
aataaacgac ttatttcttg g 1101

<210> 207  
<211> 515  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (428)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (439)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature

<222> (449)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (456)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (474)  
<223> n equals a,t,g, or c

<400> 207  
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acactgcgag aatacaaggt ggtggggcgc tgcctgcccc ccccaaatg tcgcactccg 120  
ccgctgtatc gcatgcgaat ctttgacact aatcacgtgg tcgccaagtc ccgcttttgg 180  
tactttgtgt ctacgtgaa aaagatgaag aagtcctcag gggaaatcgt ctactgtgga 240  
caggtgtttg agaaatcccc ctgcgagtg aagaacttcg gcactctggct gcgtatgac 300  
tcgagaagcg gtaccacaaa catgtaccgg ggagtaccgg ggacctgacc amcgcgggcg 360  
ccgtcaccca gtgggttaccg agacatgggc gcccacacc gttgcccag cgcattcgat 420  
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agcatttcca aggattccaa gatcaattcc cattg 515

<210> 208  
<211> 269  
<212> DNA  
<213> Homo sapiens

<400> 208  
aagcattgtg ggtaaaggcc tggaggcagg aaagtgaagg acaatttcaa gaaactcagt 60  
tcatcaattt tcatcaacac cttcctgggc catgcctggg tactgagraa cccagccctg 120  
aatctggaca tcattttccc tttagagca tagaatgcag ggggatccag ggaatgggtt 180  
aacagaagag gaagctggwt caaggagacc ttgctgacc aggtgaaggt gtttgaactt 240  
tgttcttgca ggcaggcaga gcacggaca 269

<210> 209  
<211> 734  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (278)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (732)  
<223> n equals a,t,g, or c

<400> 209  
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ccgcggacgc ccgctgagct tggcgacagg gccgaccagg agctggtgac tggcctcatg 120  
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gagaaatggt ceaagagcac cactgcccc tcggtgcccc tggcctgcgc ctggtcctgc 240  
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caccgagagc tntt 734

<210> 210  
<211> 658  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (561)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (567)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (577)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (580)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (636)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (654)  
<223> n equals a,t,g, or c

<400> 210

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gtcgggtgccg atggcgcaaa ctcgatggtg cggcgacatc tctaccgga tcatcaaatac 180
cgtaaatatg tcgctatcca gcagtgggtc gcggagaaac atccggtgcc gttctactcc 240
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agagaaaaatg agcgcctttc agttccagtt tggtaagacg gtgaaaagcg aaaaatgcac 420
gggtgctggt tccctcgcgc tggcaggatt ttgtctgcg taaggacaac gcctttcttg 480
attggtgaac ggcgggattt atcagcgcca gctcgctgga agggattagc tatgcgctgg 540
atagcacaga catttctgcg ntogtgnatc tgaacancn gagaagctca ataccgttac 600
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<210> 211

<211> 204

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (91)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (94)

<223> n equals a,t,g, or c

<400> 211

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attcggagag ccattctctga cagttagagc cgatatcact ggaagatatt caatcgtctc 60
tatgcttacg acctgcagat acagtctggt nttncacatg aagaaagtct caagttgctg 120
aagactgaat tgtaagaaaa atctccagcc cttctgtctg cagcttgaga cttgaaccag 180
agagtgtgag agctgctggt ggag 204

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<210> 212

<211> 1271

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1222)

<223> n equals a,t,g, or c

<400> 212

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caagcccagag aagacggagg aggactcaga ggaggtgagg gagcagaaac acaagacctt 120
cgtggaaaaa tacagaaaac agatcaagca ctttgccatg cttcgccgct gggatgacag 180
ccaaaagtac ctgtcagaca acgtccacct ggtgtgcgag gagacagcca attacctggt 240
catttggtgc attgacctag aggtggagga gaaatgtgca ctcatggagc aggtggccca 300
ccagacaatc gtcatgcaat ttatcctgga gctggccaag agcctaaagg tggacccccg 360
ggcctgcttc cggcagttct tactaagat taagacagcc gatcgccagt acatggaggg 420

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cttcaacgac gagctggaag ccttcaagga gcgtgtgcgg ggccgtgcc a gctgcgcat 480  
cgagaaggcc atgaaggagt acgaggagga ggagcgcaag aagcggtcgg gccccggcgg 540  
cctggacccc gtcgaggtct acgagtcctt ccctgaggaa ctccagaagt gcttcgatgt 600  
gaaggacgtg cagatgctgc aggacgccat cagcaagatg gacccaccg acgcaaagta 660  
ccacatgcag cgctgcattg actctggcct ctgggtcccc aactctaagg ccagcgaggc 720  
caaggaggga gaggaggcag gtcctgggga cccattactg gaagctgttc ccaagacggg 780  
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aaaaaaaaaa g 1271

<210> 213

<211> 1025

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (991)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1007)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1019)

<223> n equals a,t,g, or c

<400> 213

cggacgcgtg ggcgagcgtg atagccaaca ggaaccggga gcgggggtccc gggactggga 60  
agaaacggcg gccgggaggg ggctccgggg accatggggc tcctgacctt tctgaagaag 120  
atgaagcaga aagagcgagg gctgcgactg ctcatgcttg gcctggacaa tgctggaaag 180  
acaaccatcc tgaagaagtt caatggggag gacatcgaca ccattctccc aacgctgggc 240  
ttcaacatca agaccctgga gcaccgagga ttcaagctga acattctggga tgtgggtggc 300  
cagaagtccc tgcggtccta ctggcggaac tactttgaga gcaccgatgg cctcatctgg 360  
gtagtggaca gcgcagaccg ccagcgcatg caggactgcc agcgggagct ccagagcctg 420  
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caccactggg gcatccaggg ctgcagcgcc gtcaccgggg agaacctgct gccgggcac 600  
gactggctcc tggatgacat ttccagccgc attttcacag ctgactgaac cactccagat 660  
gccccccacc tagcagtcga ggtccctcaa ccttcacaa acactaccca tgggggggtg 720  
ggagtcagcc ggccaaacta acactccccc tcctccaccc cagcctgctg ctgctactgc 780  
tgcccgcgtg tgctctgtgg ccaccggct cccatggcgg gagggctgtg ccctggctgt 840

ctctctggct cctgacctgg cctttggcta ccataccaag aagagagggc tgggcgggga 900  
ggagctgcta ctgctgtac cgaggctgtg ggccatcc ttcactcagt tgtgaaataa 960  
accgctcctt gccccgmaaa aaaaaaaaaa naaaaaaaaa aaaaaanccc ggggggggnc 1020  
ccgga 1025

<210> 214

<211> 351

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (332)

<223> n equals a,t,g, or c

<400> 214

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ttagcagaag gaaggaaata gtaaatatta cagcagaagt aaagtagagg ctagaaaaat 120  
aataaaaaag atcaacaaaa tgggtattgt tctcatacta tgataaagac atacttgaga 180  
accgcattat ttatggggaa aagaagtta attgactcac agttccacag gctgtacagg 240  
aggcatggct tagggaggcc tcagggaac ttagratcca tgggtggaagg tgkargagga 300  
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<210> 215

<211> 1087

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1075)

<223> n equals a,t,g, or c

<400> 215

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actttgacat gctgtaccct gaggacagca gctgggcagc caaggcccct ggggccagca 120  
gtcgggagga gccacctgag gagcctgagc agtgcccggc cattgacagc caagcccag 180  
cgggcagcct ggacttggtg cccggcgggc tgaccttgga ggagcactcg ctggagcagg 240  
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acatcacccg agatcccatg gactggagcc ccagcaatgt gcagaagtgg ctctgtgga 360  
cagagcacca ataccgctg ccccccattg gcaaggcctt ccaggagctg gcgggcaagg 420  
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tgacgcca cctggacatc tggaagtcag cggcctggat gaaagagcgg acttcacctg 540  
gggcgattca ctactgtgcc tcgaccagtg aggagagctg gaccgacagc gaggtggact 600  
catcatgctc cgggcagccc atccacctgt ggcagttcct caaggagttg ctactcaagc 660  
cccacagcta tggccgcttc attaggtggc tcaacaagga gaagggcac ttcaaaattg 720  
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acatctycca gcgscctcgtc taccagttcg tgcaccccat ctgagtgcct ggcccaggc 900  
ctgaaacccg cctcagggg cctctctcct gcctgccctg cctcagccag gccctgagat 960  
gggggaaaac ggcagtctgc tctgctgctc tgaccttcag agccaagggt caaggagggg 1020



caaccaactg cccaggggga tatgggtcct cttggggcct tcgggaccct ggggncaagg 1080  
ggcttttc 1087

<210> 216

<211> 1977

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (11)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1873)

<223> n equals a,t,g, or c

<400> 216

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aggaggaaga tgaggaagag gaggaagaag aggaggagga ggaggaagaa gagcctcagc 120  
agcgagggca gggagagaag tcagccacgc cctcacggaa gattctggac cctaactctg 180  
gggagccagc tcccgtgctg tcctcccccac ctctgcaga cgtctccacc ttcttggtt 240  
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tggcgctgaa ccacatggtg cagcaggact atttcccaa ggcccttgca cccctgctgc 600  
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ctggscacac ctnaccagc accctgcctt tgggctgcag ctcgcttggc ttctgcgttg 1920  
ctccttcact atggaagcca cctcccttgg gatcctttgc tccactgcca catatgt 1977

<210> 217

<211> 2815

<212> DNA

<213> Homo sapiens

<400> 217

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gcttccaact agttaaatgc ccttgagcgc gggtttccgc ggccccggctc ttcgcccccg 180  
cggcgcgagt tgagccgttt ccccgcgctg tcccgcgggg cgctccgaca gcggtctctg 240  
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taacccctc ccacccctct ccatgtccgt gtgtcactcg gctcgggtcca cctggcgcg 480  
ccgggtcctg ggctgctgct gctgttgacg acgacgacga cgacgggggc tgcctctgct 540  
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cagaacctcg gcctgaccgg cactttggct ccaaaataac tttatttttg ggggagaaa 660  
cacatcacga accagtcaaa atcgtggttt atttctgtaa cgtgaagact tctgctcttt 720  
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aaaatatgaa agatttttat attttttcac tgggaagaaa ttcttcctgg atgaaattac 2340
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<210> 218

<211> 1645

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (347)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1643)

<223> n equals a,t,g, or c

<400> 218

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tggtcgggtg tttgtcgggt cccccagctg aagccaacaa gagttctgaa gatatccggt 180
gcaaatgcat ctgtccacct tatagaacaa tcagtgggca catttacaac cagaatgtat 240
cccagaagga ctgcaactgc ctgcacgtgg tggagcccat gccagtgcct ggccatgacg 300
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gagcaaacac agtcctggag cgtgtggaag gtgccagca gcggtggaag ctgcaggtgc 600
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gaggctgagc gtggatctga acaccacagc ccctgtactt gggttgcctc ttgtccctga 1440
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620  
aaaaaaaaaa aaaaaaaaaa aangg 1645

<210> 219

<211> 478

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (344)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (415)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (452)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (469)

<223> n equals a,t,g, or c

<400> 219

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gaaagtgcag gaggtgaaa tcatgtcttc ggtgctcaaa gctgccgcc atcactatgg 180  
agttcagtgt gacaagccca acaaggagtt catgctctgc cgctgggaag aaaaagaccc 240  
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<210> 220

<211> 832

<212> DNA

<213> Homo sapiens

<400> 220

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aggtagagtt aaagtcttaa tctatgcatt cagagaaata tttttatatg ctttgtgtaa 600  
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tgcatgtctg actgttcaaa cataacaagt attattaaaa ttaaatatta actgacaaaa 780  
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<210> 221

<211> 1892

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1892)

<223> n equals a,t,g, or c

<400> 221

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cctgctcatt tgaaaatctg acatcagctg ggcagtcgcc cccctcctcc ttctctccct 180  
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tttagccaca agtgactcag tggaagatcc agagtcaaca gaggtctgtc aggaagatgt 360  
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tcaaaggacc ggacaaaagag gaggaaccac cagctgtgtc atcccatggc caggggtggc 480  
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aagtcttggc aggccgtgcc cgcagctgct gctgcagttt ggggtgtctt tctgcacat 660  
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cgtttttctt tcaataaact attttgtgtc agcttcaaaa aaaaaaaaaa aaaaaaaaaa 1860

aaaaaaaaa aaaaaaaaaa aaaaaaaaaa an

1892

<210> 222  
<211> 868  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (23)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (31)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (45)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (829)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (860)  
<223> n equals a,t,g, or c

<400> 222  
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gggacatgct gctggccaat aagtgccag ctgccgcccg tgctggtgcc atagcccat 240  
gtgaggtcac tgtgccagcc cagaacactg gtctggggcc cgagaagacc tccttcttcc 300  
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attctatcat caatggatag aagcgggtcc tggctttgtc tgtggagact gattacacct 660  
ttcacttgct tgaagggtc aaggccttct tggctgatcc atctgcattt gtggctgctg 720  
cccctgtggc cgctgccacc actgctgcac ctgctgctgc tgcagcccca gccaaagtgt 780

aagcaaagga agagtcggag gaawcggatg agagkatktk camttcgana atcagcaaaa 840  
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<210> 223  
<211> 1516  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1493)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1497)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1508)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1509)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1516)  
<223> n equals a,t,g, or c

<400> 223  
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cgatggggat ggaagaggag atgcctgtga tgatgacatg gatggagatg gaataaaaaa 180  
cattctggac aactgcccac aatttcccaa tcgtgaccaa cgggacaagg atggtgatgg 240  
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taatgatctg gttggggact cctgtgacac caatcaggac agtgatggag atgggcacca 360  
ggacagcaca gacaactgcc ccaccgtcat taacagtgcc cagctggaca ccgataagga 420  
tggaattggt gacgagtgtg atgatgatga tgacaatgat ggtatcccag acctggtgcc 480  
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tatatatatt aacttcaatt ttcttttagct tttaaccaacc caaatatatc aaaacgtttt 1440  
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gggcccgnn caattn 1516

<210> 224

<211> 1306

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (148)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (887)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1242)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1264)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1303)

<223> n equals a,t,g, or c

<400> 224

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gtcggacgag gtcattggctg ccgctgcnst tacaagcctg tccaccagcc ctctccttct 180  
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ggccagtgc cagtcctctc cgtccacccc gtcaccccca ctgcccccg aggcagccca 360  
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ccgcctggtg cacctgggga ggcaggcaga gcctgatcag agtgatggtg aggaggactt 540  
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&lt;210&gt; 225

&lt;211&gt; 584

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (486)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (542)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (562)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 225

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ggaaacccag acccaagacc aaccgatgga ggaggaggag gttgagacgt tcgcctttca 120
ggcagaaaty gcscagttga tgctrytgat catcaayacy ttctactcga acaargagat 180
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gcgggcgag atatttcyat gattggccag ttcggggtcg ggttctattc ggcctacttg 480
gtggcnagaa ggtgacggtg atcaccaagc acaacgatga cgagcattac gcctgggagt 540
cntccgcagg ggctcgttca angttccgca ttgacacagt gaac 584

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&lt;210&gt; 226

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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<222> (34)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (498)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (514)  
<223> n equals a,t,g, or c

<400> 226  
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atggtgacag acatccagac tgctgtaagg accaactcca cctttgttga agctttggtg 120  
gaccatgccca aagcacagtg tgatctcctg gggcccggca tggctgacat gtgcaagaac 180  
tatatcaacc agtattcgga cattgccgtc cagatgatga tgcacatgca acccaaagag 240  
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aaggacacgg tccaggcaaa gaccagtgtt agctgtggag atatgagagt tacgtggtt 420  
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<210> 227  
<211> 2377  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (2369)  
<223> n equals a,t,g, or c

<400> 227  
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ggtccaagtc caagtccctg tcggtctcca gatctcggtc gcggtccagg tcccgggtctc 180  
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&lt;210&gt; 228

&lt;211&gt; 463

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 228

aatacatgcc aaatggatca ttaaatgaac tcctacatag gaaaactgaa taccctgatg 60  
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acaatatgac tccctcttta cttcatcatg acttgaagac tcagaatatc ttattggaca 180  
atgaatttca tgtaagatt gcagattttg gtttatcaaa gtggcgcatg atgtccctct 240  
cacagtcacg aagtagcaaa tctgcaccag aaggaggac aattatctat atgccacctg 300  
aaaactatga acctggacaa aaatcaaggg ccagtatcaa gcacgatata tatagctatg 360  
cagttatcac atgggaagtg ktatccagaa aacagcctt tgaagatgtc accaatcctt 420  
tgagataat gtatagtgtg tcacaaggac attggactgg tat 463

&lt;210&gt; 229

&lt;211&gt; 1232

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 229

cagggtgagca tctgaacaag gggcagtcgg ccagggtggg cttgcgggag tccccacctt 60  
gacctctct cttccagct gccagagcc cagaccaagc atggacgccg tggatgccac 120  
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gcagggtctg gccaaactcg ggctgggtgct ggaccaggcg gaggcagagg gtgtgtgcag 300  
gaagtgggac cgcaatggca gcgggacgct ggatctggag gagttccttc gggcgctgcg 360  
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&lt;210&gt; 230

&lt;211&gt; 1063

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 230

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&lt;210&gt; 231

&lt;211&gt; 1063

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1061)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1063)

<223> n equals a,t,g, or c

<400> 231

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<210> 232

<211> 1474

<212> DNA

<213> Homo sapiens

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<221> misc feature

<222> (1337)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1359)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1377)

<223> n equals a,t,g, or c

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<210> 233

<211> 1782

<212> DNA

<213> Homo sapiens

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<221> misc feature

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (34)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (591)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1760)

<223> n equals a,t,g, or c

<400> 233

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caaagcctgc tgggtgagca ccttgctcat tatactggwt ctgaatttac ctctttgaag 180
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<210> 234

<211> 2208

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1314)

<223> n equals a,t,g, or c

<220>

<221> misc feature

&lt;222&gt; (2189)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2202)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 234

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&lt;210&gt; 235

&lt;211&gt; 2580

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens



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<222> (1)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (3)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (2558)  
<223> n equals a,t,g, or c

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<210> 236

<211> 3008

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (3001)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3008)

<223> n equals a,t,g, or c

<400> 236

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<210> 237

<211> 877

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (834)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (854)

<223> n equals a,t,g, or c

<400> 237

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<210> 238

<211> 3039

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (177)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3039)

<223> n equals a,t,g, or c

<400> 238

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<210> 239

<211> 1992

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (12)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>

<221> misc feature  
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<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>  
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<222> (1989)  
<223> n equals a,t,g, or c

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aaaaaaaaanc cc 1992

<210> 240

<211> 497  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (387)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (476)  
<223> n equals a,t,g, or c

<400> 240  
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attgaccatt ttggagc 497

<210> 241  
<211> 316  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (133)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (311)  
<223> n equals a,t,g, or c

<400> 241  
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ccaraaagca ggcaggacgt gatggatatt gtatttatag agcaacttcc ggtaatcacc 240  
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tggcgtgggg ntaacc 316

<210> 242  
<211> 829  
<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (47)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (793)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<400> 242

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<210> 243

<211> 838

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (32)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (51)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (822)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (832)

<223> n equals a,t,g, or c

<400> 243

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<210> 244

<211> 2853

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2665)

<223> n equals a,t,g, or c

<400> 244

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<210> 245

<211> 1197

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (218)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1193)

<223> n equals a,t,g, or c

<400> 245

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<210> 246

<211> 848

<212> DNA

<213> Homo sapiens

<400> 246

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cgagtgggtcc ggcagcatgt gcgtgaggcc tctatcttgc tgggggactg accaccagc 780  
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<210> 247

<211> 1336

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1336)

<223> n equals a,t,g, or c

<400> 247

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gaagatgaag aagatgatgt gtcagagggc tctgaagtgc ccgagagtga ccgtcctgca 180  
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aaggagtga cccctgcgg accgcaccag ggccaggatg aagggcgggg gccagccccg 300  
ggcagcggca cccgccaggt gttctccatg gcagccatga acaaggaaag gggaacagct 360  
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<211> 1076  
<212> DNA  
<213> Homo sapiens

<400> 248  
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<210> 249  
<211> 2425  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (52)  
<223> n equals a,t,g, or c

<400> 249  
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<210> 250

<211> 1408

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (252)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1387)

<223> n equals a,t,g, or c

<400> 250

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<210> 251  
<211> 494  
<212> DNA  
<213> Homo sapiens

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<400> 251
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aaaaaaaaaa aagg 494
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<210> 252  
<211> 2491  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (6)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (16)  
<223> n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2457)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 252

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&lt;210&gt; 253

&lt;211&gt; 1125



&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 253

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&lt;210&gt; 254

&lt;211&gt; 1409

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 254

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<210> 255

<211> 490

<212> DNA

<213> Homo sapiens

<400> 255

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<210> 256

<211> 1233

<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

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<221> misc feature

<222> (602)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (931)

<223> n equals a,t,g, or c

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<210> 257

<211> 2404

<212> DNA

<213> Homo sapiens

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<222> (2372)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2385)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2395)

<223> n equals a,t,g, or c

<400> 257

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<210> 258

<211> 2092

<212> DNA

<213> Homo sapiens

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<221> misc feature

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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (60)

<223> n equals a,t,g, or c

<220>

<221> misc feature

&lt;222&gt; (2069)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (2071)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 258

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&lt;210&gt; 259

&lt;211&gt; 387

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

<221> misc feature

<222> (377)

<223> n equals a,t,g, or c

<400> 259

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<210> 260

<211> 3712

<212> DNA

<213> Homo sapiens

<400> 260

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<210> 261

<211> 897

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (22)

<223> n equals a,t,g, or c

<400> 261

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ccgactacct ctccccggag gagatacaga ggcagctgca ggacatcgag aggcggctgg 180  
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tgagacatga gggcgagctg cgccggctca tggccaagcc cgaggctctg aagtcactgc 420  
aggagcggcg gcgggagcag gagctgctgg agcartactg gagcaccgtg aacgaccgca 480  
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tgcgggacat gattgagaag ctgggcctcc agaggaagaa gtccaagttc cgcttgtcca 600  
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aaccgggact tgtactcggg gccgtgggct cggcccggac cgggcattcg gacttggact 780  
cgggaagggc ctctgtccc tacaaggggc atgtggacag caggacctg cgctaccgtc 840  
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<210> 262

<211> 1905

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1266)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1791)

<223> n equals a,t,g, or c

<400> 262

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tgggtgtggc tggaatgggtg gcaggagtgg gcaccagtgc gggcccgggtg gccatgggga 1860  
ataaaccagc attgctgcca aaaaaaaaaa aaaaaaaaaa aaaaaa 1905

<210> 263

<211> 1424

<212> DNA

<213> Homo sapiens

<400> 263

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gtgactgttt gattttaaaa agtgtgactg tcagttgtat ctgttgcttt tctcaatgat 180  
tcagggatag aaatgggctt ctctcattca ttaaaagaaa acgcgacatc tttctaagat 240  
tctctgtggg aaaatgactg tcaataaaat gcgggtttct gggccattcg tcttactttc 300  
attttttgat tacaaatttc tcttgacgca cacaattatg tctgctaate ctcttcttcc 360  
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gtaaaagtcc caggttctaa attaactaaa tgggtacaga aatgaacgtg taagtaatgt 480  
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gctctggagg ttcttgaaag aggggacacg aaggaggagt gactgggaag cctcccatgc 660  
caaggagggt ggagggtgcc tggaaatagc tgccctcatgc cacttaggcc atgactggat 720  
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<210> 264

<211> 1287

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (111)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (889)

<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1196)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1229)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1284)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1287)  
<223> n equals a,t,g, or c

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ccgtcccgcg gccccagcc gcccccaacc ctgccccacg ggccccggcg catgagttag 180  
ctggagcaac tgagacagga ggccgagcag ctccggaacc agatccggga tggccgaaaa 240  
gcatgtgggg actcaacact gaccagatc acagctgggc tggaccaggt ggggagaatc 300  
cagatgagga cccggaggac cctccgtggg caccctggca agatctatgc catgcactgg 360  
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tacagcctca agaccgcga ggcaacgtca gggtcagccg ggagctgcct ggccacactg 600  
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ccacctgtgc cctgtgggac attgagacag gccagcagac agtgggtttt gctggacaca 720  
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tccttgccct tccaaccaag ttngtn 1287

<210> 265  
<211> 991  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature

&lt;222&gt; (421)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (966)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 265

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ccctggagct cttccgaacc aagggtgaatg cgctcactta tggggagggtg ctgcggctgc 180
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aaaaanaaaa aaaaaaaaaa aaaaaaaaaa a 991
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&lt;210&gt; 266

&lt;211&gt; 2320

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 266

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cgcgcacaga tgggcccgggt gggcgagatt ccccgccgc ccccggaaga ctttccctg 360
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ccccaccagt ggccactcca ttcagtcca agtccagtag caagcctgca gccgggggca 720
cagcaccctt gcctccttgg aagtccctt ccagctccca gcctctgccc caggttccgg 780
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tccagaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2320
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<210> 267

<211> 423

<212> DNA

<213> Homo sapiens

<400> 267

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aggrgagctc tggagggttg acatccccct gaagctcgtg atgacgttg gcacgattg 180
tkaccatgac atgacagctg ggcgagggtc aatcgagga tttgttgcca gcatcaatga 240
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tgggctcaaa gtctgcctgc aagcggtctt gagggcttgg aatagctgca atgagtacat 360
gccagccgg atcatcgtgt accsgtggtc gtaggagacg gccagytgaa aacactggtg 420
act 423
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<210> 268

<211> 1846

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1776)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1816)

<223> n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1832)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 268

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&lt;210&gt; 269

&lt;211&gt; 601

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (536)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (556)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 269

```
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gtctcatact ctacaccagt attgctgtcc tactcaggtc cttgactcca tgaagcttac 180
cccctcaggc aggctggcag agagcagggg agaggaggag gaggaggaga ctgagggaaga 240
ggaagaggaa gacgctcacc agttctgctg tccggcctcc gagtgcagta gtccctcctc 300
tcggtaaactg agaggacaag ggccattttc tatgcagaag caaaagcctt aaccagsccc 360
tccttcccc caccaccccc cccgcagatt cccccatggg accctgtccc ctgcttcagg 420
aaccagatgg gcaagcatcg tgccccttcc tccccccacc ttcttcttgg aattcccatc 480
cccactgctg tctcctctgg actccagccc ctgaattaaa gaaactggag ccctangtcc 540
gactaaaatt tggganaagc aaacttggac ttggacttgg aactggatcc tcccgtaacc 600
g 601
```

&lt;210&gt; 270

&lt;211&gt; 880

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (876)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 270

```
aattcggcag agggaaaggg tgggggtcag cctccccaaa atcacatgga ttccccagt 60
ggaaactagg agcaggaggat tgcttgggtg gccgctaaca ccaggctact cttatttttag 120
cttgctaagt tgagatcagc tagacctgct ttcttttctc ctcagtcttg catttccctc 180
aatacaagct gcagcctctt tcctcgtttc tagtctcaga aggaaggaga gggaagccat 240
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cctctcacc ctttgccagt tccaccaact agagtgaag acttcttagc catttcatta 420
aatctattct gtatccacca ggtggcagca tcttgtcata cgtgtcagga cttaggactg 480
cggggttttag gttagatgtc acggaaaaag ctagtctgtt ggtcaggcgg caccaatgag 540
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ttgaagacct actttgtcct ctacataggg tagcttctgt cagggaatct tggttcttcc 660
caagaaacac tgattttctt tcagggagac ttcatgtgtt catttatttc caccacagca 720
gattttaaga aattataata tgtaatatat gatattctata aagagtatat ctaacgtgaa 780
taaattatga agcatactaa tgagtaccta tgaccataaa cacatatata ttaaaacatt 840
ttaaatacca aaaaaaaaaa aaaaaaaaaa aaaaanaaaa 880
```

&lt;210&gt; 271

&lt;211&gt; 2484

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (194)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (623)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2396)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2484)

<223> n equals a,t,g, or c

<400> 271

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cgatcaagtt ccttccatt tctccatctg ggggatcctg aacgtgcaca tcctcagaga 180
agccctcctg gggntctcca attctagttt attgccccct cctatcgatc cccagcgcg 240
ctcatcgggc ctgtggacaa ggacaggttt gaagagagga ttccttgat cgcggaaggg 300
ctgcaggaat ggcacagccc cttccgagga tgccaaagga gcccgggcaa aggaaagtgg 360
ccgtgccggg cctgcctacc actagatccc caccaccta tgactgctca gtcccgtct 420
cctaccacac ccacctttcc cggccdaagc cagcgcaccc cgctgactcc ctgcccagtc 480
caaactccaa ggctgggcaa ggcactgac cactgctgga cagaccggg gcagcctctg 540
ggtgaacagc agcgtgtccg ccggcagcga accgagacca gcgagccgac catgcggctg 600
cacagacttc gtgcgcggct gancgcgggt ggcctgtggg yttctgctgc ttcttgtccg 660
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```

```
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tgtaatttc cccgtttttt gggn 2484
```

&lt;210&gt; 272

&lt;211&gt; 751

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 272

```
agccaccgcg tgaccactg cccctatgcc gtggccctac ccgaggtggc ccagcccag 60
ccactcaccg aggcactgag ggctctctgc cacgtggggc tctttracat cgccttttgt 120
gccttgtttg actgcraccg cctgtggs gagaagtctt gtgacctcct tctcttcctg 180
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caaggtcaag aaatcccaca gtttgatgta ttaaagaaat gacttatctt tactcaaaat 660
aaatggcatt gaagtctttt tttaaccctt tatgagttaa tttaataata atgatctgag 720
acaaaaaaaa aaaaaaaaaa aaaaaaaaaa a 751
```

&lt;210&gt; 273

&lt;211&gt; 3309

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (3279)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 273

```
agaagcagga gggagaaggg cagacagggg tcggttgagc cagggtagaa accaagggga 60
gccagggtag aaaccaaggg gtcagggctg ggctggagga cacggctgag gtcctcccaa 120
aactgggccc atgtggtgtg acatccccac cagcctcaga tgagacgggc caggacgccc 180
agccacagca agccctgtcc ctttgccgga tccccaaaca ctagagaagc tctcctaacc 240
caaggcggag aatgaagggt gtggcggcag aggaggaggg cagcagctga gaggccaggg 300
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gtggttacac agttgacctc tgcctggctc ccccttggtg caactcctgc ctccatcccc 600
```



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cctgccaga ccaacagaga gagctgtccc tgagaccgag gagagaagca gctgccgaaa 780  
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ttcgcctaa 3309

&lt;210&gt; 274

&lt;211&gt; 843

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
<221> misc feature  
<222> (780)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (833)  
<223> n equals a,t,g, or c

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cactcccacg accagtgacc aggagttaaa ctttgggatg tgcccgtgat gttggaccac 180  
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tgt 843

<210> 275  
<211> 2028  
<212> DNA  
<213> Homo sapiens

<400> 275  
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ttgaacctct ttatagcatt gatactagggt gaacagaaat tacctgacta ataatttgtc 180  
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taattyttaa atactgttct agagttctaa aaaggcagtt ttttaaaaaa ctttaagttga 300  
taaaaactgt aagaataatt tagcagaaat agaaccagaa tgtagaagag tagtcatgta 360  
acagcagtaa taacatactt cagcttccat ataggaatag aagtggtaga gccaaaagtg 420  
atthaggaag agttataagg tacaggttga gtatcccttt tccaaaaatg cttgggacaa 480  
gaagtatttc agatttcata attttttca aagtttgga tatttgcatt atacttacca 540  
gttgggcac ccaaatctga aatctgaaat gttccatgag catttccttt gagtgtcatg 600  
ttggcactca aaaaggttca acattgagtc cacttaacac ttaggtgtta gaagacctaa 660  
ctttctgtaa caattaacct tatactttgt ttgtcatcga atatttgttg aatgcatgtc 720  
aggtaatggt cttgattgtg atagcttcaa ggtggaacat actgtaatct ccagatgcta 780  
ggaagttagt ctaataaatt actgcagaaa attgattaag tggctgtcct ttttaattaag 840  
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aaactttgat taagctgaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2028

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&lt;210&gt; 276

&lt;211&gt; 1455

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (759)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1408)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 276

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tctgctgtca gccgatcaca tcattcattg tactggaggg cgcccgagat accccacgca 600
catcgaaggt gccttggaat atggaatcac aagtgtatgc atcttctggc tgaaggaatc 660
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<210> 277

<211> 1923

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1814)

<223> n equals a,t,g, or c

<400> 277

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ttgtggaagc attgagcaaa tccaaggcag aactcatgga aatcagtga gataaaacta 420  
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aagaatggtt agaagataaa ggtcaagtac taaatattca gatgagaaga acattgcata 600  
aagcatttaa gggatcaatt tttgttgtgt ttgatagcat tgaatctgct aagaaatttg 660  
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aggctgggct ttgnatattt acacaggaaa gttgggtaac actagaaata attacttggt 1860

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gga 1923

<210> 278  
<211> 1380  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (1293)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1297)  
<223> n equals a,t,g, or c

<400> 278  
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tttctcttca ttccagatc ctttatttca gagcagccca tttcctctg gattcattga 180  
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atgaggcctt catgaacggt taccttctcc atacactagg gaagcatttg tcagactctg 300  
cagactgggt tctagagagg cagagtcttt aagagtattc atttcttctg gaagggtggag 360  
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aattaaattt taaggagatt cttatctaata aactttgtgt gtgcttttgg atacaggctg 1260  
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<210> 279  
<211> 1018  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (818)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1017)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1018)

<223> n equals a,t,g, or c

<400> 279

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ttcgcgctcg gcttgctcgg cgggagctcg tctcgatgct agcccgcgag ctaccgcgcg 180
ccgtcgcccc tgcggggcca gctagcttag cgcgctggac gctgggcttc tgcgacgagc 240
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caccgccaca gcgtgtgacc ctcacrtac ctgtcctgaa tgcagcacga actgtcatct 600
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aaaacccgct gcccgcgcgc ctggtccagc cccacaccgg gaaactgtgc tggttcttgg 720
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ctccggccag cagccctacc cggggctcaa cacacaggct gtggctctgg acatccggat 960
attaaaagga gcgttgctgg aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaann 1018
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<210> 280

<211> 1192

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1105)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1130)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1154)

<223> n equals a,t,g, or c

&lt;400&gt; 280

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ggtttactta atcaggacat gggcctaaga acaaaccctt tcccttcacg ataacatcca 180
tagacaactt attagaaggg actagagttt ttgcaaattt ccttgctgga tggggcctat 240
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catatccact tcttcccagt ctgccttggg attaaagcac caagcagaga ccacattaat 600
tccctttgct atactgtgat ccttagtatg ttaattctta agaaaccaac atatcactga 660
aagaaggctg gcagaacgca agtgcatttt ttcactgtgg gaagaaagat caagtgcagt 720
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&lt;210&gt; 281

&lt;211&gt; 1755

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 281

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agtcgtctat aaaaactcat ctctgcgctt ctcttcgcca cattcgcttc ctgctttcgg 180
tgtgtctgtt gtgtcttgtt gggggcaccg cagtcgacct gaagatggcg tctaccagcc 240
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acagaatcaa tctacctcga aatatagttg atcgaacaaa taatttatcc aagcaagtat 660
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tttctaagaa agaaattggg cgggtgttta aacttatttt gaaagcgcta gaaaccagt 840
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ataatgcaaa tcattgcagc taataaagct gatagacttt atttccatta cttatatata 1560  
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acatcaacat catagtttcc agtttgaaag gatgtgtatg tgagatttat tatgtatatt 1680  
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<210> 282

<211> 1093

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (90)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (970)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1081)

<223> n equals a,t,g, or c

<400> 282

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<210> 283

<211> 1556



<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1324)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1339)

<223> n equals a,t,g, or c

<400> 283

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<210> 284

<211> 1029

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (828)

<223> n equals a,t,g, or c

<220>  
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<222> (958)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (972)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (976)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (987)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1007)  
<223> n equals a,t,g, or c

<400> 284  
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<210> 285  
<211> 1583  
<212> DNA  
<213> Homo sapiens

<220>

<221> misc feature  
<222> (1411)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1531)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (1557)  
<223> n equals a,t,g, or c

<400> 285  
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gccgagctga ccaacaggac acacagattc ctggagaaaag ccaaggcctt gaagatcagt 180  
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gaggaagcag agaaactgat taaagatgtt acagaaatga tggctcaagt agaagtga 360  
ttatctgaca caacttccca aagcaacagc acagccaaag aactggattc tctacagaca 420  
gaagccgaaa gcctagacaa cactgtgaaa gaacttgctg aacaactgga atttatcaaa 480  
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<212> DNA  
<213> Homo sapiens

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aattacgaca ttttaagata tttcatagac aaaccaaaaca aaaatatatg tttttacttt 660
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<210> 287

<211> 506

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (394)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (470)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (481)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (494)

<223> n equals a,t,g, or c

<400> 287

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taggtgttcc ctagtgtttc ttaatttctt tttagaaagt gtatttttat tagtattttt 180
ccggtgaaca gaagatttgt ttggatttaa acatttacta agacagtacc tattaggaaa 240
accaaattat gcaaatggct aattcgattt taatttctca aaagatactc tgttatccag 300
aagattaaaa tgcctacatt gagtgcttaa aaaaaaaaaa acmactgtga tratktgagc 360
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nggggaaatt ttanccctat aaaatt 506

<210> 288  
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<212> DNA  
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<222> (3)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (926)  
<223> n equals a,t,g, or c

<400> 288  
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tcaagcttaa attgaagttt aaattcatct ataaccaaat caaatgatca gaggaaattc 840  
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<210> 289  
<211> 1034  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (376)  
<223> n equals a,t,g, or c

<400> 289  
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gccattgggg gccttggaaa ccagccatgt ctttgggct ctgtggagag ctttagcctt 180

gcacggcggc gctgggaggc attgcctgcc atgcccactg cccgctgctc ctgctctagt 240  
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<210> 290

<211> 3091

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (24)

<223> n equals a,t,g, or c

<400> 290

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agctaccccc aggaacagca cctgacaggc gggggatttt ttttcaagtt gttctacatt 300  
tgcataaaatt atttctatta ttattcatgt atgttattta tttctgaatc aactagtc 360  
tgtgaaagta caactgcaag gcagaaagtg ttaggatttt gcatctaattg ttcattatca 420  
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&lt;210&gt; 291

&lt;211&gt; 518

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 291

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taacagtcga gaaacaaaaa aaaaaaaaaa aaaaattc 518

&lt;210&gt; 292

&lt;211&gt; 498

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

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<222> (482)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (489)  
<223> n equals a,t,g, or c

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gntccaagnt tagttacg 498

<210> 293  
<211> 469  
<212> DNA  
<213> Homo sapiens

<400> 293  
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<210> 294  
<211> 668  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (568)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (650)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (652)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (658)  
<223> n equals a,t,g, or c

<400> 294  
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ttgttttc 668

<210> 295  
<211> 1400  
<212> DNA  
<213> Homo sapiens

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<210> 296

<211> 960

<212> DNA

<213> Homo sapiens

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<220>

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<222> (859)

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<220>

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<222> (933)

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<220>

<221> misc feature

<222> (950)

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<222> (959)

<223> n equals a,t,g, or c

<400> 296

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<210> 297

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (86)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<400> 297

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&lt;210&gt; 298

&lt;211&gt; 892

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 298

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&lt;210&gt; 299

&lt;211&gt; 1624

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1621)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1623)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1624)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 299

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nann

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&lt;210&gt; 300

&lt;211&gt; 1969

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (13)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 300

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<210> 301

<211> 1882

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (22)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (223)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1840)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1849)

<223> n equals a,t,g, or c

<400> 301

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ggaataaaaa taacaaaaaa at 1882

&lt;210&gt; 302

&lt;211&gt; 2804

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 302

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<210> 303

<211> 3859

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (581)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (889)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (890)



<223> n equals a,t,g, or c

<400> 303

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (588)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (664)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 307

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&lt;211&gt; 2171

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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<213> Homo sapiens

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<222> (6135)

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<222> (6158)

<223> n equals a,t,g, or c

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&lt;210&gt; 310

&lt;211&gt; 2086

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1763)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1769)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 310

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&lt;210&gt; 311

&lt;211&gt; 2163

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 311

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&lt;210&gt; 312

&lt;211&gt; 1397

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1397)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 312

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<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (344)

<223> n equals a,t,g, or c

<400> 313

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<210> 314

<211> 532

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (497)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (498)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (502)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (524)

<223> n equals a,t,g, or c

<400> 314

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ccatgcccga gtgtcccaag tgcaacaagg aggtgtactt cgccgagagg gtgacctctc 180
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ggtggtggag accccatcct tggctgcttg cagggccact gtccaggcaa atgccaggcc 420
ttgtccccag atgccagggt ctcccttggt gcccctaata ctctcagtaa acctgaacac 480
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```

<210> 315

<211> 1938

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1270)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1455)

<223> n equals a,t,g, or c

<400> 315

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gcggctgcgg gcagccgagg cggccgaggc ggcggcgggc gcggcggcgg ccggcagcgg 180
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gaatgccacg gacagggtaa cccagtgcga gtacaaacgc atcggtgccc catggcacgg 540
cccttccat gagctgacgg tgcacgaggc tgcgtgcgcc caccgacca agacaggcag 600
tgagctgatg gagatcctgg atgggatgga ccagagccac cgcaaggaga tgcagctgta 660
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caacagcadc ttcagcctgc tcagcttcga gaagattggc tacacagagg tccagttccg 720  
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agggtcagc aggcattttc ggaaagcagg gtgaaattgt ctcttcccag gaaaaagatt 1860  
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cgcatctag aactagtc 1938

<210> 316

<211> 818

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (55)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (818)

<223> n equals a,t,g, or c

<400> 316

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cccagcaact caaattcacc acctcgact cctgcgaccg catcaaagac gaatttcagc 180  
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cagagatgca gcgtcactat gtgatgtact acgagatgtc ctacggcttg aacatcgaga 300  
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<210> 317

<211> 837

<212> DNA

<213> Homo sapiens

<400> 317

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tgtgagccgg actcaggcgg atcttgacag ccttgtccgc gagtgcgcgc ggatagaacc 180  
cgtgtgcgtg gacctgggtg actgggaggc caccgagcgc gcgctgggca gcgtggggcc 240  
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caaggaggcc tttgacagat cctttgaggt gaacctgcgt gcggtcatcc aggtgtcrca 360  
gattgtggcc aggggcttaa tagcccgagg agtcccagg gccatcgtga atgtctccag 420  
ccagtgtcc cagcgggcag taactaacca tagcgtctac tgctccacca aggggtgccct 480  
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ggccaagact atgctgaacc gaatcccact tggcaagttt gctgaggtag agcacgtggt 660  
gaacgccatc ctctttctgc tgagtgaccg aagtggcatg accacgggtt ccactttgcc 720  
ggtggaaggg ggcttctggg cctgctgagc tccctccaca cacctcaagc ccatgccgt 780  
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<210> 318

<211> 1448

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (878)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1198)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1395)

<223> n equals a,t,g, or c

<220>

<221> misc feature



&lt;222&gt; (1397)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1445)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 318

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gcggctgtga agtgaggggg tctaggggag aaaaggggac ggagagcaga ggaaggggtg 240
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aaacntgg 1448
```

&lt;210&gt; 319

&lt;211&gt; 1493

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 319

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taacttctcg ctgactgctt cacctcttac aagtctgccc atcccggaag taatgatgac 120
aaaatactcc aaccttttct tggaaagtca taacatctca ctgactgaac attccagtg 180
gccagtggaa aaaaatatca ctttagaacg accttctgct gtagaactca catgtcagtt 240
cacaacttct ggggatgtga attcagtaaa tgtgacttg gaaaaagggg atgaacaact 300
taagaattac catgtcagtg ccacagaagg catcctgtat acccagtaca agttttccat 360
cattaatagc gaacaactgg gaagctattc ttgtttcttt gaagaggaaa aggaacgaag 420
gggcacattt aatttcggag tcctgaagt tcagagaaaa aacaaacat tgatcactta 480
tgtgggggat tccgttgtct tgggtgtgaa atgccgacac tgtgtcctt taaattggac 540
ctggtacagt ggtaatagga gtgtacaggt tcctcttgat gttcacatga atgaaaagta 600
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attaagaaat gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaagggcggc cgc 1493
```

&lt;210&gt; 320

&lt;211&gt; 609

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 320

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ggcacgagtg gcttctgacc ctttcttccg ccactaccgc cagctcaatg agaagctagt 60
gcagctcatc gaagactata gccttgtctc ctttatccct ctcaacatcc aggacaagga 120
gagcatccag cgagtcctgc aggtctgtgga taaagccaat ggatactgtt tcggagccca 180
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ttattttct 609
```

&lt;210&gt; 321

&lt;211&gt; 502

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (458)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 321

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ctgaggtgaa ctgaagccag cagccccgca tcatgtcaaa gtcgggcccg gccgcccggg 120
gcctcaggaa gcccgaggtc ggcgggtgtra tccgggcgat cgtgcgggca ggccctggcca 180
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gcaaggagtt caatgagagg acaaaggaca tcaagggaagg cattcctctg cctaccaaga 300
tttttagtgaa gcctgacagg acatttga aaagattgg acagcccact gtttcctact 360
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tcctgaaggc agcagctggg attgaaaagg gggcccggca aacagggaaa gaggtggcag 420  
gcctgtgtac cttgaagcat gtgtatgaga ttgcccgat caaagctcag gatgaggcat 480  
ttgcctgcag gatgtacccc tg 502

<210> 322

<211> 2630

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1952)

<223> n equals a,t,g, or c

<400> 322

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acccttccgg caccctctgga cagcccagga tgctgttggc caccctcctc ctctcctcc 180  
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<211> 1874

<212> DNA

<213> Homo sapiens

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<222> (1735)

<223> n equals a,t,g, or c

<400> 323

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<210> 324

<211> 2325

<212> DNA

<213> Homo sapiens

<400> 324

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caagatgaga taaagacatt ttgatacagt aattgttttg gttgggtttt catgtcagtt 360  
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2325

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<212> DNA

<213> Homo sapiens

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ttgacttaag atcccacacc tcacaaacct acagcccaga aaccagaagc ccctatagag 720  
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<211> 244

<212> DNA

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gacgacagaa ggggtacggc gcgagaagac kacagaaggg tacggctgcg agaagackac 180  
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<211> 2454

<212> DNA

<213> Homo sapiens

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&lt;211&gt; 505

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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aaagagaaac tttttcccag ctgggtgctg tggctcacac ctgtgaatcc cagccctttg 180  
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<211> 559

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<213> Homo sapiens

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ttagttgcac tagccatatt tcaaatactt gatggataca tgtggctagt ggctaacata 180  
agggatagca cagatataaa acatttcctc ccaaagtgtt gggattacag gcatgagcca 240  
ccgcgccccg cctatcatat gaattttgag ggaacacaat catgcagtct gtagcagatg 300  
gtaaataggct gatataattac acttgttgat gtaanctgga tangtttctt tcttctccaa 360  
ggacagcttt ttnaatattt aacantncca ttaatttttc agtttccggg agaattttat 420  
aattttaaatt tgccgactta ngganaanc aattggncca accattacaa tanattttta 480  
attccgntta aaaaatccca ccngnggggg aattccgctt aaaattttat tttccattat 540  
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ctggncagac accgntgnaa cgggnattat ttcaccctca gagagaggct gatcactatg 180  
caaaaacaac tgggaggaaa ccagagaagta tattgaatga gcagtgacaga ttagagttgc 240



ccatatacgat gggcancaat tgncaattat tgtgnagcaa tacacacggg gtttccangg 300  
gagtnttaaa tgccttaaag taattaaaaa ccggggcaat nccnttttac ggatgttttg 360  
ctgggggttc cgtttttaac caacattttt ntnggggncc gnccacaaat tttgggggtg 420  
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aatgtngcca ntgtctgtct gcagattggc tacccaactg ttgcatcagt accccattct 180  
atcatcaacg ggtacnaacg antcctggcc ttgtctgtgg agacggatta caccttccca 240  
cttgctgaan aagtcanggc ttcttggtgc atccatctgc cttngtggct gctgccngt 300  
tggtgctgc caccacaact gtcctgctg ctgctgcnc ccancttaag ttnaaaccca 360  
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tcacggccac cgtcatcctt gtctcggccg ggggaagccta cctggtgtac acagaccggc 240  
tctattctcg ctcggaactc aacaactacg tggctgctgt atacaagggtg ctggggactt 300  
cctgtttggg gctgccgtga gccagtctct gacagacctg gccaaagtaca tgattgggcg 360  
tctgaagccc aattctaanc gtctgcgaac ccgattgaac cggtaaatgc tcgtnatgtg 420  
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catcaaagtc tactacacct tgagaaaaca aatgaacgan aatctatattt cctcattcat 180  
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cccggaaagc gaagtggaag aaagtcttag tggcttgaga ttaagcctga tcaagatgac 180
aacctcccaa aagcaccgag acttcgtggc agancccatg ggggagaacc agtggggaac 240
ctggctggga ttggtgaant cctgggcaag aaactggaag aaagggtttt gacaaggcta 300
tnttgtcttg gccatttctg gtgctaaaaa anataaaaac tctcccggaa tggtgaaaaa 360
ctttttgggc caccacaacat ccggaatgtc cgatgctcca aaatgtgcan cctcttttat 420
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caattcactg gccgtcggtt tacaacgctg tgacnnggaa aacntnnaat ncttcgggt 180  
cgtatgttgt gtggaattgt naggcgataa caattcacac aggnancagc tataaccatg 240  
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gttnaacaag ntcaaccatg naagngtttc anctnaatgg gggggncccc gtaaccceat 300  
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cagcaccatg aagatcaaga tcattgcccc tccggaggcg caaatactct gtctggatcg 180
gtggctccat cctggcctct ctgtccacct tccagcagat gtggatcagc aaacagggaa 240
tacgggtgaag cggggccttc cattgtccac cgcaaagtct ttcttaaaac acttttcctg 300
gttcctnttc tgtcttttag gcacacaact gtggaatgtn cctgtgggaa tttatggccn 360
tttcagtttc tttttccaaa tcattcctag ggccaaagt ttgnattggt tnanccatgg 420
ggttttttta aataaantnt ggaaataggg ttaattggtt aaaaaaaann nnaaaaaaaa 480
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tgcattgggg gtgtcatcct cttccatgag acactctacc agaaggcgga tgatgggcgt 300
cccttcccc aagttatcaa atccaagggc ggtgttgtgg gcatcaaggt agacaagggc 360
gtggtcccc tggcagggac aaatggcgag actaccacc aagggttgga tgggctgtct 420
gagcgtgtg cccagtacaa ngaaggacgg agctgacttc ggccaagtgg cgttgtgtgc 480
ttaagaatgg gggaacacac ccctcannc ctnggcacat tggaaaatgc caattgntct 540
ggccccgtat gccagtatct ggcancagaa tgcattgggc cattcgggga gtctgananc 600
tcctgatggg ancatgactt gaa                                     623
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<210> 339

<211> 344

<212> DNA

<213> Homo sapiens

<220>

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<222> (88)

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<222> (157)

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<220>  
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<223> n equals a,t,g, or c

<220>  
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<220>  
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<222> (343)  
<223> n equals a,t,g, or c

<220>  
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<222> (344)  
<223> n equals a,t,g, or c

<400> 339  
tcgacccacg cgtccgcttc aacatgattt gtcacaatct tatcaataat cattactctg 60  
ttttttatat ttcaactaaa agtatcanaa tatagctttc cagaaaaccc cgaaccaaag 120  
tcactgacta catcaaagtc tactacacct tggaganaac aaatgaacga naatctattt 180  
tcctcattca ttacccaac aataataggn ctccctatcg taattattat cactatgttt 240  
ccaagcatta tattcccatc acctaccga ctaatcaata atcgactcat ctccattnca 300  
acaatggatt agtgcantga acatgcaaan gcaaggatta tcnn 344

<210> 340  
<211> 345  
<212> DNA  
<213> Homo sapiens

<220>  
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<223> n equals a,t,g, or c

<220>  
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<222> (13)  
<223> n equals a,t,g, or c

<220>  
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<222> (31)  
<223> n equals a,t,g, or c

<220>  
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<222> (88)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (90)  
<223> n equals a,t,g, or c

<220>  
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<222> (128)  
<223> n equals a,t,g, or c

<220>  
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<222> (135)  
<223> n equals a,t,g, or c

<220>  
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<222> (138)  
<223> n equals a,t,g, or c

<220>  
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<222> (146)  
<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c



<220>  
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<223> n equals a,t,g, or c

<220>  
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<220>  
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<222> (313)  
<223> n equals a,t,g, or c

<220>  
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<222> (339)  
<223> n equals a,t,g, or c

<220>  
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<222> (343)  
<223> n equals a,t,g, or c

<220>  
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<222> (345)  
<223> n equals a,t,g, or c

<400> 340  
agacangctc tantacgact cactataggg naaagctggt acgcctgcag gtaccgggtcc 60  
ggaattcccg ggtcgaccca cgcgtccngn aggaggggac agctgcgggc gcggggaggg 120  
ggcgcccgnc cgcgngngnc catggnggac agnagagccg ggagtcagag annccgggcc 180  
gcagcccag atgtcgccgc catggcttcg ccgcagctct gccgcgcgt ggtgtcggcg 240  
caatgggtgg cggaagcgt gcggggcccc cgcgctgggg cagcctctgc agctgntagg 300  
acgcctcctg gtnacctggc cggaagctgg ggggcgcgna cgncn 345

<210> 341  
<211> 170  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (20)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (43)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (86)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (160)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (163)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (164)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<400> 341

acccacgcgt cgcgccacgn tcncgactag ttctagatcg cgnacggccg ctctagagga 60  
tccaagctta cttggacatg catgcnacgt catagctctt ctatagtgtc acctaaattc 120  
aattcactgg cgtcgtttt acaacgtcgt gactgggaan atnntaaaaan 170

<210> 342

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (238)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (273)

<223> n equals a,t,g, or c

<220>  
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<222> (328)  
<223> n equals a,t,g, or c

<220>  
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<222> (337)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (351)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (366)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (384)  
<223> n equals a,t,g, or c

<400> 342  
aatgacttgg ttgagtactc accagtcaca gaaaagcatc ttacggatgg catgacagta 60  
agagaattat gcagtgtctc cataaccatg agtgataaca ctgcggccaa cttacttctg 120  
acaacgatcg gaggaccgaa ggagctaacc gcttttttgc acaacatggg ggatcatgta 180  
actcgccttg atcgttgga accggagctg aatgaagcca taccaaacga cgagcgtnac 240  
accacgatgc ctgtagcaat ggcaacaacg ttngcaaact attaaactggc ggactactta 300  
ctctagcttc ccggcaacaa tttatagnct tgggtgnggc gggtaaagtt ncaaggccca 360  
tttttnggtt tggccttcgc gttngtt 387

<210> 343  
<211> 186  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (26)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (64)  
<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (71)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (109)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (152)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (153)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (160)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (183)  
<223> n equals a,t,g, or c

<400> 343  
gctgcaggaa attaacagag tctacnagga aatgtacaag actgatctgg agaaagacat 60  
tatntcggac ncatctggtg acttccgcaa gctgatgggt gccctggcna aagggttaaaa 120  
aacagaagaa tgggccgtcc ttgaatatga anngaatan ccacatgccc ggatttcctt 180  
ganccc 186

<210> 344  
<211> 611  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (8)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (11)  
<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<400> 344

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tgcaaggnga nactaccctc actaaaggga acaaaagctg gagctccacc gcggtgcggc 60
cgctctagaa ctagtggatc ccccgggctg caggaattcg gcacgagctg cgttgggctc 120
cggaagccg ttcgggctgg ggctgtcggc cgcggggcgg aggcactcgc gcgggggatg 180
gcccactcgc tgaccttggg tcagctgtcc atttctgtg accatctcat tgacaaggac 240
atcggctcca agtctgacct actctgcgtc cttttacagg atgtnggagg gggcagctgg 300
gctgagcttg gccggactga acgggtgcgg aactgctcaa gccctgagtt ctccaagact 360
ctacagcttg agtaccgctt tgagacagtc cagaagctac gctttggaat ctatgacata 420
gacaacaaga cgccagagct gagggatgat gacttcttag ggggtgctga gtgttcccta 480
ggacagattg tgtccagcca ggtactgact ctccccttga tgctgaagct ggaaaacctg 540
ctgggcgggg gaccatcacg gtctcagctc aggaattaaa ggacaatcgt gtagtaacca 600
tgagagtaga g                                     611
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<210> 345

<211> 344

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (296)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (329)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (342)

<223> n equals a,t,g, or c

<400> 345

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tttccttcta cagtattcct gaatttgacg aatggaaaaa acatatagaa aaccagaaag 60
cctggaaaat aaagtactat aaaggattgg gtactagtac agctaaagaa gcaaaggaat 120
atattgctga tatggaaagg catcgcatct tgtttagata tgctggctct gaagatgatg 180
```

ctgccattac cttggcattt agtaagaaga agattgatga cagaaaagaa tgggtaacaa 240  
atatttatgga agaccggaga cagcgtagct acatggctta ccagaggant gattcnctct 300  
caactcagac atgaaagatc tataccacnc ntgttgatgg cntt 344

<210> 346

<211> 506

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (392)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (452)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (453)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (472)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (480)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (495)

<223> n equals a,t,g, or c

<400> 346

ggaaaagccc aaggaaaaag caaagaatag caaaaaaag ggggccaaga aggaagtggg 60  
tgggattggg cttctttttt cttcagtgag ttttttcccc aacaggttct gatggtcctt 120  
tggctaccag caaaccagtc cctgcagaaa agtcaggtct tccagtgggt cctgagaacg 180  
gagtagaact ttccaaagag gagctgatcc gcaggaagcg cgaggagttc attcagaagc 240  
atggggaggg tatggagaag tccaacaagt ccacgaagtc agatgctcca aaggagaagg 300  
gcaaaaaagc accccgggtg tgggaactgg gtggctgtgc taacaaagaa atgttgatt 360  
acagtacttc caccaccaat ggaaccctg angcttgctt tgtctgagga cattaacctt 420  
gattccaagg gactgggtct ggggggcact tnnngatctg gactgcacac tntgatgacn 480  
aagggttgt taaantttcc aaacta 506

<210> 347

<211> 444  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (289)  
<223> n equals a,t,g, or c

<400> 347  
cggaaggag accatgttcc gagcggcggc tccggggcag ctccggcggg cggcctcatt 60  
gctacgattt cagagtaccc tggtaatagc tgagcatgca aatgattccc tagcaccat 120  
tactttaaat accattactg cagccacacg ccttggaggt gaagtgtcct gcttagtagc 180  
tggaacaaaa tgtgacaagg tggcacaaga tctctgtaaa gtagcaggca tagcaaaagt 240  
tctggtggct cagcatgatg tgtacaaagg cctacttcca gaggaactna caccattgat 300  
tttggcaact cagaagcagt tcaattacac acacatctgt gctggagcat ctgccttcgg 360  
aaagaacctt ttgccagag tagcagccaa acttgagggt gccccgattt ctgacatcat 420  
tgcaatcaag tcacctgaca catt 444

<210> 348  
<211> 358  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (19)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (52)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (187)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (280)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (295)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature

<222> (301)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (317)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (348)  
<223> n equals a,t,g, or c

<400> 348  
ggcagagaag cagaagcgnc tcagttagag tccagcaaaa ggtttgccaa anagtttatg 60  
gacagacatg gaatcccaac cgcacaatgg gaaggctttc accaaacctg aaaggaagcc 120  
tgcagcttca ttttgagtgc agacttcctt gctttggttg tgaaaggcca gtggtcttgc 180  
agctggnaaa aggggtgatt gttgcaaaga gcaaagaaga ggcctgcaag ctgtacaaga 240  
gatcatgcag gtaggctggg tcttctggaa aaatttactn ttgtattcat actgnatgaa 300  
ntaccgtttt aagtttnaaa aatgttcctc acattaaggg aaattctntt ttgcaacc 358

<210> 349  
<211> 321  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (187)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (206)  
<223> n equals a,t,g, or c

<220>  
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<222> (240)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (294)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (295)  
<223> n equals a,t,g, or c



<220>  
<221> misc feature  
<222> (301)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (316)  
<223> n equals a,t,g, or c

<400> 349  
ggcgcgtttgc tctgtccacc aagattcctg acaccaaagg ctgcttgag tgctcgtgtgg 60  
tgccggaaccc ctacacgggt gccacettcc tgctggccgc cctgcccacc agcctgctcc 120  
tgctgcagtg gtagtgagccg ctgcagaagt ttctgctgct gaagaacttc tccagccctc 180  
tgcccanccc agctgggatg ctgganccgc tgggtgctga tgggaaggag ctgccgcagn 240  
gtttttttgg ggccgaaggg cctaaagggc ccggttgccg gttcctgttc caannccctgc 300  
ncctgggagg ttggcnttaa g 321

<210> 350  
<211> 742  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (618)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (653)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (658)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (683)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (689)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (702)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (707)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (714)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (719)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (722)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (734)

<223> n equals a,t,g, or c

<400> 350

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ggtcacgctg acccagtgtt cggaagagct ggtgcagctc atcctgcacg aatacaagat 60
cttcaatgca gaagtgtttt tccgagaaga ctgtcccccg gacgagttca tcgatgtgat 120
cgtgggcaac cgggtgtaca tgccctgcct gtatgtttat aacaaaatcg accagatctc 180
catggaagag gtggaccgcc tggcccgaaa acccaacagt gtggtcatca gctgcgcat 240
gaagctgaac ctggactatc tgctggagat gctctgggag tacttgccc tgacctgcat 300
ctacaccaag aagagaggac agaggccaga cttcacagac gccatcatc tccggaaagg 360
ggcctcagtg gagcagtggt gcaccagcac caagtacagt ccgcagcggg tgggcctgac 420
ccacaccatg gagcatgagg acgtcatcca gatcgtgaag aagtaacggc gcctgccggg 480
ccttccgccc acctgtcgt ctcccttggg aggtggtccc actgggacac acaaacacc 540
aaacagaaaa atacaaatac acgtacccca agaaggggtc cctcaagtct ctgctattta 600
cagaagtttc ttcagtangc agacaaaaaa tgtgttgggc aaaagggctc ggntggangc 660
atthtccata agactgagcc ctnttcatng ggggttttga gnttgantgc ttancctgna 720
tntgtgcctc caanccctg ac 742
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<210> 351

<211> 272

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (167)

<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (251)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (272)  
<223> n equals a,t,g, or c

<400> 351  
aatcaggcgg gactgacggc agatcgtatg ctggctcctgt ccagagccgg gcaggcggca 60  
gggctgacgt ttaaccagac cagcgagtca ctcagcgcac tggttaaggc gggggtaagc 120  
ggtgaggctc agattgcgtc catcagccag agtggtggcg gttctctnctc tgcacccggc 180  
gtggagggtgg acaaggctcg tgaagccttc gagggggggcc cgtacccatt tgcctatagt 240  
aagcgtatta naataattgc cgtgttttaa an 272

<210> 352  
<211> 256  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (170)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (236)  
<223> n equals a,t,g, or c

<220>  
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<222> (248)  
<223> n equals a,t,g, or c

<220>  
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<222> (251)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (252)  
<223> n equals a,t,g, or c

<400> 352  
gcagacgtcc agagcagagt cagccagcat gaccgagcgc cgcgtcccct tctcgtcct 60  
gcggggcccc agctgggacc ccttcgcga ctggtaccgc catagccgcc tcttcgacca 120

ggccttcggg ctgccccggc tgccggagga gtggtcgcag tggtaggcn gcagcagctg 180  
gccaggctac gtgcgcccc tgccccccgc cgcacgcaga gcccgcagc ggccgngccc 240  
gctacagncg nncgct 256

<210> 353  
<211> 592  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (35)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (54)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (93)  
<223> n equals a,t,g, or c

<220>  
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<222> (277)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (480)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (485)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (522)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (545)  
<223> n equals a,t,g, or c

<400> 353  
ggttcccttc cacgctgtgg aagcattgta ctttnggtct tcatgataaa tctngctgct 60

gctcactcgt tgggtccgtg ccacctttaa aancgtgaac actcaccgag aaggtctgca 120  
acttcactcc tggggccagc aagaccacga gtgcaccgag aggaatgaac aactctggac 180  
acaccatctt taagaaccgt aatactcacc gcaaggtctt gcaacttcat tcttgaagtc 240  
agtgaaggcca agaaccatc aattccgtac acatttnggt gactttgaag agactgtcac 300  
ctatcaccaa gtggtgagac tattgccaag cagtgaact attgccaagt ggtgagacca 360  
tcaccaagcg gtgagactat cacctatcgc caagtgggtc taagtgtgaa cgtgaagtcc 420  
ccagccctgc tgctgagcca gttgctgccc tacatggaga acaagaaggg tgctgtcatn 480  
ctggncctct ccattgcagc ttataatcca gtagtggcgc tnggtgtcta caatgtcagc 540  
aaganagagc tgctggggtc tcactagaac actggcattg ggcttgcccc cc 592

<210> 354

<211> 539

<212> DNA

<213> Homo sapiens

<220>

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ccttcaacat gccggaacca gcgaagtccg ctcccgcgcc caagaagggc tcgaagaaag 180  
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cgtgcgcctg ctgctgcccc gggagtgggc caagcacgcc gtgtccgagg gcaccaaggc 480  
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ggtccctgtg gtactcagag tatcgcttcc ctgaagaact cactcagacc ttcattgagct 180  
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gccaggagct tgcctttccg ctgagtccag attggcaagt ggactacgaa gtcatacaca 360  
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gaaccccggtg gaacagaggc agcgcacatc cggagggcaa aaagccangg ggatagtggg 180
ggcggtttttg cagtaagga cccgaacact gatcgctggg tggccacggg catcgtgtnc 240
ctngggcatc gngtgcagca gggccttatg gcttnttaca ccaaagtnc cnaacttncg 300
tggccttgga tcaagnnaga cctngganca ggaggactnc cgccccanca ttcactaggt 360
tcnaatcca gngagcagtt tcgcanaaan canccanaca cancttcccc ctntttngnn 420
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aaagaatccg cataccagga agggcgctgg gaaacactgc ctttcagcg ggccatcatg 180  
aatgcgaatg ggcagcgact acatccgtga gtggaatgtg gtgaagtttg cccgtntcgg 240  
ttattccaaa atgctgctgg gngtttatgc ctactttata gggcataagc agnggaacan 300  
ccttatttgg tttccncagg atggtggatg cccgagaant ttttggaana cccacgttgn 360  
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taaatttttt gctgacctgc tggattacat caaaggactg antagnaaat agtgnataga 180  
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gtttgaggta cataagaaaa atgtaagggg tgaattcact tattatgaaa tacaagataa 180  
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actcaatect gattcaagta tggaaacttc accagacttt ttcttctaaa atctggatgt 420  
cattgacgat aatgtttatg gagataaggt ctaagtgcct aaaaaaatgt acatatacct 480  
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aaatggggta tntggagnnc ttttttaatt ttcatagnt ttttttnat aanaatggca 600  
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agacgcggca atacagcgggt atctgggacg gaacgnntaa accggcatac agcaacaaca 180  
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cagactggag gagttttcga aagantggaa ggatgccagt nataagtga atgccatgtg 180  
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248

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&lt;211&gt; 149

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;221&gt; misc feature

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&lt;223&gt; n equals a,t,g, or c

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&lt;210&gt; 364

&lt;211&gt; 352

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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aatagtagca ttgtctgacg ctgctgtaga acctattgat ttccaattg ctccgtgata 180  
tgctgcatct atggtnctta aagatgtggg attgaaaaa gaagatattg caatgtggga 240  
agtaaatgga agcctttagt ctggtgtac tagcaaacat taaaatggtt ggagattgga 300  
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<400> 365

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ctggcaaacc anggacagac caggnacatg ggaccaaagc cggaacctcc tgctcaacgg 180
gaagtcctan ccaccaaag tgcgcctgat ctgggggggc tccctncccc cagtcaagcg 240
gncggcggat gaactggatn nacgccccgg at 272
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<211> 254

<212> DNA

<213> Homo sapiens

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cccgggtcga cccacgcgct cgcttctctg cctagaaggg ataattattat cactcttcgt 120
tataataaca atcaccatct taattaacca ccttacatta gccagcataa cccctatcat 180
ccttcttgta tntgcagcct gtgaagcnnn actgggggctt atccctttta gttatnatct 240
caantacata cgga 254
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<210> 367

<211> 185

<212> DNA

<213> Homo sapiens

<400> 367

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tgcagagaac gttgaatgcc tggaaattaat cacattcccc tggttcagag ctgtacgtgg 120
aaaccatgag caaatgatga ttgatggcct atcagagcgt ggaaacgtta atcactggct 180
gctta 185
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<210> 368

<211> 458

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ccggagtgag ccttgaacgc ctggacctgg acctcacagc tgacagccag ccacccgtct 120  
tcaaggtcctt cccaggcagt accactgagg actacaacct tattgttatn gaacgtggcg 180  
ctgccgctgc acnaccggcc agccaggagc tgcgcctgca ggaacccctg gngccccacc 240  
cctggntggn atggccattg tcaaggagga ggagacggag gctgccattg gagccccctcc 300  
tactgccact gagggncctg agaccaaacc tgtgcttatn gctcttgagg agggtccttg 360  
tgctgagggt tcccggctgg actcactagt ggcanaacna ctcnngctgg aagtngtagc 420  
tctgaggagc tcngecccag tgttgcccg gacctgat 458

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<220>  
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ccccgcctgc ngccctgttt gcaactcgcc tgtagtgctt gentagggcc cgcngccccg 120  
ccgcgcgcaa cagctcgggg gacggcgggg cggcgggcga cggcacctg gtggactgtc 180  
ccgtgtgcaa gcaacagtgc ttctccaaag acatcgtgga gaatnatttc atgcgtgana 240  
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<220>  
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ntcctccgcc gpcgcggact ccggcagctt ttcgccaga ntccctgaac tctcgctttc 120  
tttttaatcc cctgcacggg ntcaccggcg tgccccacca tgtcagacgc agccgtagac 180  
accagctccg aaatcaccac caaggactta aaggagaaga aggaagtttt ggaaagaggc 240  
agaaaatgga agagacggcc ctnccttaacg gggaatgcta atttagggaa at 292

<210> 371  
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<213> Homo sapiens

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<220>  
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<400> 371  
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tggttccaag cataaaagaa cggacagatc aattttatgt tgtttacgaa aaggagaatc 120  
tggccagtca tggcaagggt taacaaaaga aagggcaaag cttaattggc ttagtgtcga 180  
cttcaataat tgggaaagac tgggaagatg attcaaatga agacatgtct aattttgaat 240  
cgtttctctg aggattcaca agacagtgat gatggnaaaa atgccagatc tgggagtaag 300  
ggaatattgt ccntcacctg ggtttttgag gaaaggaaaa tnaactttct ctggcaagggt 360  
tttcataat ttgngaggaa ttccccgagt ttgttagcnc cttaaaggcn gttatgetcg 420  
tatttgnccc actntaacc ctttttnnca nccggtttgt ttttttaaaa gggcttc 477

<210> 372  
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<400> 372

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agaaganatc cttnaccctt gtaggaatgt ttttgaact aaatttnatg aacgtnaaat 120
ttncagtggt ttattatgaa cttccttgtc gaagttgaaa ggtgaacaac nctnatattg 180
caaataccgt agagcttcag agtgcaagat tctccactgn angttgggca ttcacaaatg 240
ttggatcttt cccaccgtgg gatgaagggt tcagaggcat tgcacccaaa atnaccggg 300
tgaacatacc cagnccaaag cccaggggna cattnatcgn ggacaggccc nccagaattt 360
ggcntgttct ttncagttg gtaggtgtgg aacttggggg tgaattnatt ncttaaccga 420
attnnccgn ttccttaacc gag 443
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<211> 464

<212> DNA

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<222> (235)

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<400> 373

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gagacttggg gatggaaccg cacagagccg cgggcccttt gcagctgcga ttttcgccct 120
acgttttcaa cggaggtact atactggcaa ttgctggaga agattttgca attgttgctt 180
ctgatactcg attgagtga gggttttcaa ttcatacgcg ggatagcccc aaatnttaca 240
aattaacaga caaacagtc attggatgca gcggttttca tggagactgt cttacgctga 300
caaagattat tgaagcaaga ctaaaagatgt ataagcattc caataataag gccatgacta 360
cgggggcaat tgctgcaatg ctgtctacaa tcctgtattc aaggcgcttc ttccatact 420
atgtttacaa catcatcggt ggacttgatg aagaaggaaa gggg 464
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<210> 374

<211> 369

<212> DNA

<213> Homo sapiens

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<220>  
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agagccgcgg gccctttgca gctgcgattt tcgccctacg ttttcaacgg aggtactata 120  
ctggcaattg ctggagaaga ttttgcaatt gttgcttctg atactcgatt gagtgaaggg 180  
ttttcaattc atacgcggga tagcccaaa tgttgncnna ntaacagaca aaacagtcac 240  
tggaatgcagc ggttttcatg gagactgtct tacgctgaca aagattattg aagcaagact 300  
aaagatgtat aagcattcca ataataaggc cntgactacg gggggcaatg ctggcangcn 360  
gtntctacan 369

<210> 375

<211> 313  
<212> DNA  
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gtacacaacc gcccaactgc tggcggcaaa tgagcagaaa ttttaagtttg atccgctgtt 120  
tctgctctc tttttccgtg agagctatcc cttcaccacg gaggaagtc tatctctcac 180  
aaattccggg actggtaaac atggcgctgt acgtttcgcc gattgtttcc ggtgaagggt 240  
atcccgttnc cctggcggtt tccacctntg aatttaaggc cgggataatg tcnaagcccc 300  
aagcatgnaa gtg 313

<210> 376  
<211> 375  
<212> DNA  
<213> Homo sapiens

<400> 376  
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gtccaggggc cgacagcgcc caggcgggca gaggggcttc atgtcaggga tgccccaacc 120  
agcggctgtg cgcttctgga gcgggggcca ctccggacac ggctatagag gaaatcaaag 180



agaaaatgaa gactgtaaaa cacaaaatct tggattgtc tgggaaaggc ggtgttgga 240  
aaagcacatt cagcgccac cttgcccac gcctagcaga ggatgaaac acacagattg 300  
ctcttctaga catcgatata tgtgggccat cgattcccaa gataatggga ttggaaggag 360  
agcaggttca ccaga 375

<210> 377

<211> 434

<212> DNA

<213> Homo sapiens

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<222> (381)

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<222> (409)

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gacngagana gtncagaagc tgtgcccagg ggggcagntc ccattcctgc tntatgnac 120  
tgaagtgcac acagacacca acaagnttgc ngaatttctg nangcagtgc tgtgccctcc 180  
caggtacccc aanctggcag ctctgaaccc tnantccaac acagctgngc tgganatatt 240  
tgncaaattn tctgcctaca tnnnnanttc aaaccacagna ctcaatgaca atctggagaa 300  
nggactcctg aaagccctgn acgttttagn caattantta acatccccc nctcagaaga 360  
agtggatgan accagtgtg nagtgaagggt gtctctcaga agaagttnt ggatagcacg 420  
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<220>  
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<223> n equals a,t,g, or c

<220>  
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<222> (492)  
<223> n equals a,t,g, or c

<220>  
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<222> (493)  
<223> n equals a,t,g, or c

<220>  
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<222> (496)  
<223> n equals a,t,g, or c

<220>  
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<222> (503)  
<223> n equals a,t,g, or c

<400> 378  
aattttcact cccctcagaa cataacatag taaatggatt gaattatgaa gaatgggttt 60  
tatgcgactt accgcagcaa aaataaagg aaagataagc gctcaataaa cctgtctgtt 120  
ttccttaatt ctntgctggc tgataatcat cacctgcagg ttggctccaa ttatttgtat 180  
attcataaaa tcgatggaaa aacttttctc ttaccacaaa caaatgacaa gagtctggtt 240  
cagaagataa atcgctctaa agcttcagtt gaagatatta agaacagcct cgtngatgac 300  
ggaatcattg ggattcccat cttttttgtt tgttgaaggc gacaccattg gtttttgcca 360  
gaactgnntt tcgggncggc cacatncgnt ttgacaggt ttttttaatc ggggaaggga 420  
ntgtccttaa ggcgtggggn gcngttcagt tggggccctg ttggggggac cnccaaggng 480  
gtggttatgg cnnngntttc atnggc 506

<210> 379  
<211> 550  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (6)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (9)  
<223> n equals a,t,g, or c

<400> 379  
gacganacna accctcacta aaggggaacaa aagctggagc tccaccgagg tgcggccgct 60  
ctagaactag tggatccccc gggctgcagg aattcggcac gaggccatcc agactgagga 120  
agaccgggaa acttaggggc cacgtgagcc acggccacgg ccgcataggc aagcaccgga 180  
agcaccgccg cggccgcgggt aatgctggtg gtctgcatca ccaccggatc aacttcgaca 240  
aataccaccc aggtactctt gggaaagttg gtatgaagca ttaccactta aagaggaacc 300  
agagcttctg cccaactgtc aaccttgaca aattgtggac tttggtcagt gaacagacac 360  
gggtggaatgc tgctaaaaac aagactgggg ctgctcccat cattgatgtg gtgcgatcgg 420  
gctactataa agttctggga aagggaagc tcccaaagca gcctgtcatc gtgaaggcca 480  
aattcttcag cagaagagct gaggagaaga ttaagagtgt tggggggggc tgtgtcctgg 540  
tggcttgaag 550

<210> 380  
<211> 573  
<212> DNA  
<213> Homo sapiens

<220>  
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<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (6)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (10)  
<223> n equals a,t,g, or c

<220>  
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<222> (160)  
<223> n equals a,t,g, or c

&lt;400&gt; 380

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aagncnagan agccaaccct cactaaaggg aacaaaagct ggagctccac cgcggtgcgg 60
ccgctctaga actagtggat cccccgggct gcaggaattc ggcacgagcg caaagaaggg 120
tggcgagaag aaaaagggcc gttctgccat caacgaaggc taacccgaga atacaccatc 180
aacattcaca agcgcaccca tggagtgggc ttcaagaagc gtgcacctcg ggcactcaaa 240
gagattcggg aatttgccat gaaggagatg ggaactccag atgtgcgcac tgacaccagg 300
ctcaacaaaag ctgtctgggc caaaggaata aggaatgtgc cataccgaat ccgtgtgcgg 360
ctgtccagaa aacgtaatga ggatgaagat tcaccaaata agctatatac tttggttacc 420
tatgtacctg ttaccacttt caaaatttct gtgctaaaca gtgttacagt cgccaagagc 480
ccataaaggg agccctctcg gaagtggatg aggccttggg tctcggtctt tcattgcttc 540
ctgagctgca gcagatgcct ttacaaccaa gct 573
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&lt;210&gt; 381

&lt;211&gt; 531

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (5)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (8)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 381

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gcagnacnaa ccctcactaa agggaacaaa agctggagct ccaccgcggt gcggccgctc 60
tagaactagt ggatcccccg ggctgcagga attcggcacg aggcggcggt ggcggttgt 120
gcagcaatgg ccaagatcaa ggctcgagat cttcgcggga agaagaagga ggagctgctg 180
aaacagctgg acgacctgaa ggtggagctg tcccagctgc gcgtcgccaa agtgacaggc 240
ggtgcggcct ccaagctctc taagatccga gtcgtccgga aatccattgc ccgtgttctc 300
acagttatta accagactca gaaagaaaac ctcaggaaat tctacaaggg caagaagtac 360
aagcccctgg acctgcggcc taagaagaca cgtgccatgc gccgccggct caacaagcac 420
gaggagaacc tgaagaccaa gaagcagcag cggaaggagc ggctgtacct gctgcggaag 480
tacgcggtca aggcctgagg ggcgcattgt caataaagca cagtggctga g 531
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&lt;210&gt; 382

&lt;211&gt; 300

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (1)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature



<222> (5)  
<223> n equals a,t,g, or c

<220>  
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<222> (40)  
<223> n equals a,t,g, or c

<220>  
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<222> (43)  
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<220>  
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<222> (59)  
<223> n equals a,t,g, or c

<220>  
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<222> (171)  
<223> n equals a,t,g, or c

<220>  
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<222> (172)  
<223> n equals a,t,g, or c

<220>  
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<222> (175)  
<223> n equals a,t,g, or c

<220>  
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<222> (179)  
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<222> (184)  
<223> n equals a,t,g, or c

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<222> (190)  
<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (271)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (292)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (293)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (300)

<223> n equals a,t,g, or c

<400> 382

ngggngtacc acaaataaa ggcaaagagg aactgctggn cangagtacg ggggtgtggnc 60  
atgaatcctg tggagcatcc ttttgagggt ggcaaccacc agcacatcgg caagccctcc 120  
accatccgca gagatgcccc tgotggccgc aaagtgggtc tcattgctgc nngcnggant 180  
ggangtctcn ggggaaccaa gantgtgcag gagaaagaga actagtgcgt agggcctcaa 240  
taaagtttgt gtttatgcc aaaaaaaaaa naaaaaaaaa aaaaaaaaaag annaaagagn 300

<210> 383

<211> 475

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (36)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (146)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (363)

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<220>

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<222> (367)  
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<222> (401)  
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<222> (404)  
<223> n equals a,t,g, or c

<220>  
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<222> (415)  
<223> n equals a,t,g, or c

<220>  
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<222> (450)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (451)  
<223> n equals a,t,g, or c

<400> 383  
atgacgcccgg tgcagcggggg gggcccgggg gcctgngtg ccctgggatg gggaaccgcg 60  
gtggcttccg cgaggtttcg gcagtggcat ccggggccgg ggtcgcggcc gtggacgggg 120  
ccggggccga ggcgcggac tcgcgnaggc aaggccgagg ataaggagtg gatgcccgtc 180  
accaagtttg gccgcttgg caaggacatg aagatcaagt ccctggagga gatctatctc 240  
ttctccctgc ccattaagga atcagagatc attgattctt cctgggggct ctctcaagga 300  
tgagttttga agatatgcca tgcagaagca gaccctgccg gccacgcacc agttcaagca 360  
ttnttgnaac gggattaaat gccactcgtt tggtttaatg nccnagagtg gcacncatcc 420  
tgggcaaaaac tggcaaatct caagtccttn naagtatggg gaaaatggaa cccaa 475

<210> 384  
<211> 127  
<212> DNA  
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<220>  
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<222> (5)  
<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (62)

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<220>

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<222> (71)

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<220>

<221> misc feature

<222> (103)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (124)

<223> n equals a,t,g, or c

<400> 384

caatntgnag accagattcc taaggctgca naggggacag tgggatctat ttaggaccg 60  
angagattaa ncagagacac aggcaattgt atgtcagcag ctngatttaa cccacctaaa 120  
aggngcg 127

<210> 385

<211> 317

<212> DNA

<213> Homo sapiens

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<222> (30)

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<222> (151)

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<220>

<221> misc feature

<222> (187)

<223> n equals a,t,g, or c

<220>  
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<222> (203)  
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<220>  
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<222> (231)  
<223> n equals a,t,g, or c

<220>  
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<222> (264)  
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<220>  
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<222> (308)  
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<220>  
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<222> (311)  
<223> n equals a,t,g, or c

<220>  
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<222> (316)  
<223> n equals a,t,g, or c

<400> 385  
ggcacgaggg atgtgcgacg tgtgcctggn gtagcccca ctctgtacg gtcggcatct 60  
gagaccagtg agaaacgccc ctatcatgtgt gcttaccag gctgcaataa gagatatttt 120  
aagctgtccc acttacagat gcacagcagg naagcacact ggtgagaaac cataccagtg 180  
tgacttnaag gactgtgaac gangttttct cgttcagacc agctcaaaag ncaccaaagg 240  
aggacataca ggtgtgaacc attnccagtg taaaattggt cagcgaaatt ctcccgtcc 300  
gaccaacnga ngaccna 317

<210> 386  
<211> 433  
<212> DNA  
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<220>  
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<220>  
<221> misc feature

<222> (311)  
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<220>  
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<222> (359)  
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<220>  
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<222> (385)  
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<220>  
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<222> (405)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (407)  
<223> n equals a,t,g, or c

<220>  
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<222> (427)  
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tcccgggtcg acccacgcyt ccgccgagag ccttagccga cggaaactgg acactggaac 120  
cggcagcgcc atgagactcc tcccccgctt gctgctgctt ctcttactcg tgttccctgc 180  
cactgtcttg ttccgaggcg gccccagagg cttgttagca gtggcacaag atcttacaga 240  
ggatgaagaa acagtagaag attccataat tgaggatgaa gatgatgaag ccgangtaga 300  
agaagatgaa nccacagatt ttgtagaaga taaagaggaa gaagatgtgt ctggtgaanc 360  
tgaaacttta ccgagtgcag atacnactat actgttttta aaggngnaga ttttccgcca 420  
ataacantgt gaa 433

<210> 387  
<211> 407  
<212> DNA  
<213> Homo sapiens

<220>  
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<220>  
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<220>

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<222> (359)

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<220>

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<222> (373)

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<220>

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<222> (376)

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<222> (407)

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<400> 387

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ggtgacgggt ctgtacgacg tgcaggcttt caagtttggg gacttcgtgc tgaagagcgg 120
gctttcctcc cccatctaca tcgatctgcg gggcatcgtg tctcgaccgc gtcttctgag 180
tcaggttgca gatattttat tccaaactgc caaaaatgca ggcacagtt ttgacaccgt 240
gtgtggagtg ccttatacag ctttgccatt ggctacagtt atctgttcaa ccaatcaaat 300
tccaatgctt attanaagga aagaaacaaa ggattatgga actaagcgtc ttgtanaang 360
aatattaatc canganaaac tgtttaatca ttgaaatgtt gtcccan 407
```

<210> 388

<211> 244

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (215)

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<220>

<221> misc feature

<222> (221)

<223> n equals a,t,g, or c

<400> 388

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ttcgttcac tatcgatcg ccacactcac aacaatgagt ggcagatata gcctgggtggt 60
tcaggcggcg catTTTTatt gctgtgttc gctgtaattc ttctatttct gatgctgaat 120
caatgatgtc tgccatcttt cattaatccc tgaactgttg gttaatacgc ttgaggggtga 180
atgcgaataa taaaaaagga gcctgtagct ccctnatgat nttgcttttc atgttcatcg 240
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ttcc

244

<210> 389  
<211> 239  
<212> DNA  
<213> Homo sapiens

<220>  
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<220>  
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<222> (21)  
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<220>  
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<220>  
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<220>  
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<220>  
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<220>  
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<222> (163)  
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<220>  
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<222> (185)  
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<220>  
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<220>  
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<222> (202)  
<223> n equals a,t,g, or c

<220>  
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<222> (205)  
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<400> 389  
nggactggcg tcagacgtcg nattccggcg cccacggctcg gcttaaaccg tggtncaatc 60  
ctgncgcccc ncgatgatgcc agggaaagaca gggcgacctg gaagtccaac tacttnctta 120  
agatcatnca acgtattggg atgattatcc taaaatgggt tcnattggtg ggtagcgagt 180  
acganatggt ggggcntcct anagntagta tggcgagcta gagtccccgc taatgttcc 239

<210> 390  
<211> 382  
<212> DNA  
<213> Homo sapiens

<220>  
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<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (54)  
<223> n equals a,t,g, or c

<220>  
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<222> (69)  
<223> n equals a,t,g, or c

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<220>  
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<222> (126)  
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<220>  
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<222> (169)  
<223> n equals a,t,g, or c

<220>  
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<222> (192)  
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<220>  
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<220>  
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<222> (345)  
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<220>  
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<222> (346)  
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<220>  
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<222> (360)  
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<220>  
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<222> (374)  
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<400> 390  
tcaangcgca attaacccctc actaaagggg acaaaagctg ggaacgatct ggtntctctg 60  
cgcgctgcnc gcacactgag gccgcccggg acaaagcccg gnntcggngc gacctttggt 120  
cccggnctca gtgagcgagc gagcgcgagc agagggagtg gccaaacttna tcactagggg 180  
ttccttgtag tnaatgatta acccgccatg ctacttngnc nacgtagcca tgggntacca 240  
agctcgagct ctctagactc gacgcgcgta atacgactca ctatagggcg aatttgagct 300  
ccaccgcggt tgcggccgct ctactagagt cgacctcatg gnttnncccc gaaaccgcgn 360  
aacacccgct gacncgcct ta 382

<210> 391  
<211> 375  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (6)  
<223> n equals a,t,g, or c

<220>  
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<222> (7)  
<223> n equals a,t,g, or c

<220>  
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<220>  
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<222> (70)  
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<222> (104)  
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<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (146)  
<223> n equals a,t,g, or c

<220>  
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<222> (159)  
<223> n equals a,t,g, or c

<220>  
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<222> (208)  
<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (261)  
<223> n equals a,t,g, or c

<220>  
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<222> (269)  
<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

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<222> (370)

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<400> 391

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cgggtgcagn tgccaggggtg gcctgagcga tctacggatg ggcngtatgg agtggangag 120  
acgagatgcg ggtgttanag caggginctga ccggagtgn acacatgagt gtcaggtgca 180  
ggtagtccga gtcggcgaca tgagcctnga gtagagtcac cantcgatga gatctggagg 240  
caactggcga gcaagaccgt ntgggtgcant gtcantcang ctgttgacagg tgagagcant 300  
gcactcgtcg agtggcgaga cagatcaatc tctgttagcg ggtggagggt ncactcgcgc 360  
tgtggnggtn cactg 375

<210> 392

<211> 121

<212> DNA

<213> Homo sapiens

<220>

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<222> (3)

<223> n equals a,t,g, or c

<220>

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<222> (9)

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<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>  
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<220>  
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<223> n equals a,t,g, or c

<220>  
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<222> (113)  
<223> n equals a,t,g, or c

<220>  
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<222> (118)  
<223> n equals a,t,g, or c

<220>  
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<222> (120)  
<223> n equals a,t,g, or c

<400> 392  
gantcatcng agngtggtga tttagagccgc cgcatttttt aaccctaaat ctcganatgc 60  
atcgtgnttc ctgtccattg gactgtaagg tttatgtagg catcttgga acnatggan 120  
a 121

<210> 393  
<211> 83  
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<213> Homo sapiens

<220>  
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<220>  
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<223> n equals a,t,g, or c

<220>

345

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<223> n equals a,t,g, or c

<400> 393  
ggcagagaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60  
aaaanncccn ggngggggcc ccc 83

<210> 394  
<211> 218  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (13)  
<223> n equals a,t,g, or c

<220>  
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<222> (64)  
<223> n equals a,t,g, or c

<400> 394  
gtcggcgag aangcgcccc gcacccccgc caggcgcatg tctgcacctc cgcttgccaa 60  
aggncctcgg tcagcgactg gatgetcgcc atcaaggtcc agtggagtt cttcaagagg 120  
aaaggcgccc ccgccccagg cttccgcgcc cagcgctcgc cacgetcagt gcccgtttta 180  
ccaataaact gagcgacccc aaaaaaaaaa aaaaaaag 218

<210> 395  
<211> 83  
<212> DNA  
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<220>  
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<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (13)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (83)  
<223> n equals a,t,g, or c

<400> 395  
aattcggcac ngnaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aan

83

&lt;210&gt; 396

&lt;211&gt; 70

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (69)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 396

aattcggcac agaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60  
aaaaaaaaana 70

&lt;210&gt; 397

&lt;211&gt; 140

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (50)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (57)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (74)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (93)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (113)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (114)

&lt;223&gt; n equals a,t,g, or c



<220>  
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<222> (115)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (139)  
<223> n equals a,t,g, or c

<400> 397  
aatttgacca gagaacaaga ataaccgcgc ctcagcgccg ggttttcttn gcctcangat 60  
cgcccccaaa acanataacc aattgtattt atngaaaaat aaatagatac aannnactaa 120  
acatagcaat tcagatctnt 140

<210> 398  
<211> 157  
<212> DNA  
<213> Homo sapiens

<220>  
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<220>  
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<220>  
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<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>  
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<222> (123)  
<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (134)  
<223> n equals a,t,g, or c

<220>  
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<222> (150)  
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<400> 398  
aattcggcan agctcaagca gacggggctc aaggggggtta catttaataa aaggatgaag 60  
atggnaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120  
nnnccngggg gggncceccc ccccccttn cccctt 157

<210> 399  
<211> 358  
<212> DNA  
<213> Homo sapiens

<220>  
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<223> n equals a,t,g, or c

<220>  
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<222> (84)  
<223> n equals a,t,g, or c

<220>  
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<222> (204)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (207)  
<223> n equals a,t,g, or c

<220>  
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<222> (302)  
<223> n equals a,t,g, or c

<220>  
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<222> (305)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature

<222> (308)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (341)

<223> n equals a,t,g, or c

<400> 399

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gcaagcgcca tatgagcctg gcgncgcca tagcgaatcc tgttgtggg tttttgcct 120
attcccgccc ctacgtcttg ccgggatggc accgcccgc taggacttcc agggttggg 180
tgagtgggag ttcgactgct gggncctngta attctcgctt tgggggctgc tccttccagg 240
ctggggacac actggggccc gttgttcggt ctcccgctct cgcacatctt gtctggaact 300
tncgncctngc agtttcata ggagtggag nctgtgcggc ntaattttg tggaaaaa 358
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<210> 400

<211> 399

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (15)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (33)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (46)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (70)

<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

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<222> (117)  
<223> n equals a,t,g, or c

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<222> (169)  
<223> n equals a,t,g, or c

<220>  
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<222> (171)  
<223> n equals a,t,g, or c

<220>  
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<222> (213)  
<223> n equals a,t,g, or c

<220>  
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<222> (216)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (218)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (231)  
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<220>

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<222> (245)  
<223> n equals a,t,g, or c

<220>  
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<222> (248)  
<223> n equals a,t,g, or c

<220>  
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<222> (255)  
<223> n equals a,t,g, or c

<220>  
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<222> (262)  
<223> n equals a,t,g, or c

<220>  
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<222> (269)  
<223> n equals a,t,g, or c

<220>  
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<222> (279)  
<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

<220>  
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<222> (292)  
<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

<220>  
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<222> (325)  
<223> n equals a,t,g, or c

<220>  
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<222> (349)  
<223> n equals a,t,g, or c

<220>  
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<222> (364)  
<223> n equals a,t,g, or c

<220>  
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<222> (382)  
<223> n equals a,t,g, or c

<400> 400  
tttttttttt ttttnaaaag ggcacanata cantttttacc gtttanacca aaccagaatc 60  
aaaacccean tcagagtatc canaaatcca agccagggtca aaacaaaaac gaaantntca 120  
agcaatccaa atcaagtcaa aaacaaaaac caaagtgccg gtacaggcnt nccgtgggtg 180  
atcaggccac ccttccactc aaatggagtg ggnaantncc aaagactagt nttaccaant 240  
ttcanatntc cggantccaa gngcctgtnc ctcccagng ttnagccgct gnattgatcc 300  
tctgtggggg cctgcnaaac gccantctgg cgagggtgtc cactggggna attgcctacc 360  
cggnagtgtc ctcaggttct gngtccctca agctggcca 399

<210> 401  
<211> 189  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (1)  
<223> n equals a,t,g, or c

<220>  
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<222> (11)  
<223> n equals a,t,g, or c

<220>  
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<222> (162)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (165)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (166)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (187)  
<223> n equals a,t,g, or c

<400> 401  
naattcggca nagcaaacca caccttctct ttcttatgtc tttttactac aaactacaag 60  
acaattgttg aaacctgcta tacatgttta ttttaataaa ttgatggcaa aaaaaaaaaa 120  
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa anccnngggg ggggcccccc 180  
ccccccntt 189

<210> 402  
<211> 174  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (10)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (73)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (103)  
<223> n equals a,t,g, or c

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<222> (107)  
<223> n equals a,t,g, or c

<220>  
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<222> (130)  
<223> n equals a,t,g, or c

<220>  
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<222> (132)  
<223> n equals a,t,g, or c

<220>  
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<222> (146)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (149)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (167)  
<223> n equals a,t,g, or c

<400> 402  
aattcggcan agctgaggca ggagaatcgc ttgaattcgg gaggcagagc tgagatcaca 60  
cctctgacac tcnagcctgg gtgacagagc gagactccgt ctnaggnaag gaaaaaaaaa 120  
aaaaaaaaan cncggggggg gcccngtnc ccaattggcc ctatagnngg tcgt 174

<210> 403  
<211> 263  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (5)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (231)  
<223> n equals a,t,g, or c

<220>  
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<222> (236)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (242)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (252)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (260)  
<223> n equals a,t,g, or c



&lt;400&gt; 403

ggcanagecca acccagcagt ccttccctca gctgcctagg aggaagggac ccagctgggt 60  
ctgggaccac aaggaggag actgcacccc actgcctctg ggccctggct gtgggcagag 120  
gccaccgtgt gtgtcccgag taaccgtgcc gttgtcgtgt gatgccataa gcgtctgtgc 180  
gtggagtccc caatgaaacc tgtgtcctg cctgggcaaa aaaaaaaaaa naaanaaaaa 240  
anaaaagaaa anaaaaaaan aaa 263

&lt;210&gt; 404

&lt;211&gt; 478

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (159)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (259)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (427)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 404

tcgacccacg cgtccggggg ctgcagcatg ttgctgagga gtgaggaata gttgagcccc 60  
aagtcctgaa gaggcgggcc agccaggetg acatctgtgt ttcaagtggg gctcgccatg 120  
ccgggggttc ataggctact ggctctccaa gtgccagang tgggcagggt gtggcactga 180  
gccccccaa cactgtgccc tgggtggagaa agcactgacc tgtcatgccc cctcaaacc 240  
tcctcttctg acgtgcctnt tgcacccctc ccattaggac aatcagtccc ctcccatctg 300  
ggaagtcctt tttcttttct accctagcca ttcttggtac ccagccatct gcccaagggt 360  
gccccctcct ctcccatccc cctgccctcg tgggcagccc ggctgggttt gtaaatgtgg 420  
gttgtgnaca gtgatttttt cttgtattta aaaaaggcca gcattgtggt tcattaaa 478

&lt;210&gt; 405

&lt;211&gt; 223

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (147)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; misc feature

&lt;222&gt; (158)

&lt;223&gt; n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (172)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (217)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (223)  
<223> n equals a,t,g, or c

<400> 405  
agacagcagg acggtggcca tggaagtcgg aatccgctaa ggagtgtgta acaactcacc 60  
tgccgaatca actagccctg aaaatggatg gcgctggagc gtcggggcca taccggtccg 120  
tcgccggcag tcgagagtgg acgggancgg cgggggcngc gcgcgcgcgc gncgtgatgg 180  
tgtgcgtcgg agggcggcgg cggcggcggg ggtgtgnngt ccn 223

<210> 406  
<211> 104  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (8)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (37)  
<223> n equals a,t,g, or c

<220>  
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<222> (81)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (93)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (103)  
<223> n equals a,t,g, or c

<400> 406  
cccacgcntc cgccgacagc agcagcctca ccatgangtt gctgatggtc ctcagtctgg 60  
cggccctctc ccagcactgc nacgcaggct ctngctgccc ctna 104

<210> 407  
<211> 66  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (17)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (21)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (57)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (66)  
<223> n equals a,t,g, or c

<400> 407  
gccctatagt gagtctngta ncaattcact ggccgtcggt ttacaacgtc gtgacgngga 60  
aaactn 66

<210> 408  
<211> 278  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (6)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (19)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature

<222> (252)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (275)  
<223> n equals a,t,g, or c

<400> 408  
gggcanagca agctcctgna cctcaagtga tccacatgcc ttggttgacc aaattgctgg 60  
gattacaggc atgagccaat atgaccagct caaacatctt ctttttaaata gtcagaagca 120  
tgtatagtga ttatttctta ttttttcccc cttgatccat ctcaccagat gtttggtgat 180  
tttataagaa ttttcaaact accagcttct ggctttgttg aacttgggat ttctgtttca 240  
ctaattttct tncctctgtc ttgtacttac ttgntgg 278

<210> 409  
<211> 168  
<212> DNA  
<213> Homo sapiens

<220>  
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<222> (16)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (38)  
<223> n equals a,t,g, or c

<220>  
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<222> (127)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (140)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (143)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (145)  
<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (167)  
<223> n equals a,t,g, or c

<400> 409  
aataaaactc taaaangatc actataaaaa aagcaggacgc ctgcaggt accggtccgg 60  
aattcccggg tcgaccacg cgtccgacgg ctgcgagaag acgacagaag ggcacggctg 120  
cgagaanacg acagaagggn gcnantgaaa gaaggcggca gaaaggnt 168

<210> 410  
<211> 415  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (307)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (347)  
<223> n equals a,t,g, or c

<400> 410  
tgaataccta agatttctgt cttgggggttt ttggtgcatg cagttgatta cttcttattt 60  
ttcttaccaa ttgtgaatgt tgggttgaaa caattaatga agcttttgaa tcatccctat 120  
tctgtgtttt atctagtcac ataaatggat taattactaa tttcagttga gaccttctaa 180  
ttggttttta ctgaaacatt gagggaacac aaatttatgg gcttcctgat gatgattctt 240  
ctaggcatca tgctctatag tttgtcatcc ctgatgaatg taaaattaca ctgttcacaa 300  
agggttngtc tcctttccac tgctattaat catggtcact ctcccnnaaa tattatattt 360  
tttctattaa aagaaaaaaa tggaaaaaaa ttacaaggca atggaaacta ttata 415

<210> 411  
<211> 636  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (383)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (512)  
<223> n equals a,t,g, or c

<220>  
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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (544)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (547)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (583)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (599)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (603)

<223> n equals a,t,g, or c

<400> 411

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gcagatcaga cgtggcgacc cgctgaattt aagcatatta gtcagcggag gagaagaaac 60
taaccaggat tccctcagta acggcgagtg aacaggggaag agcccagcgc cgaatccccg 120
ccccgcggcg gggcgcgagg catgtggcgt acggaagacc cgctccccgg cgccgctcgt 180
ggggggccca agtccttctg atcgagggcc agcccggtgga cgggtgtgagg ccggtagcgg 240
cccccgggcg gccggggccc ggtcttcccg gagtcggggt gcttgggaat gcagcccaa 300
gcgggtggtg aactccatct aaggctaaat ccccttgtaa atttaactgt tagtccaaag 360
aggaacagct ctttgagcac tangaaaaa ccttgtagag agagtaaaaa atttaacacc 420
catagtaggc ctaaaagcag ccaccaatta agaaagcggt caagctcaac acccactacc 480
taaaaaatcc caaacatata actgaactcc tnacaccena ttggaccaat ctatcaccct 540
atanaanaac taatggtagt ataagtaaca tgaaaacatt ctnccttcgca taagcctgng 600
tanattaaaa cacttgaact gaccattaac aggcca 636
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<210> 412

<211> 182

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (129)

<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (166)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (169)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (170)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (172)  
<223> n equals a,t,g, or c

<400> 412  
ccattgattt ttatcaatag tcgtattcat acggatagtc ctggtattgt tccatcacat 60  
tctgaggatg ctcttcgaac tcttcaaatt cttcttccat atatcacctt aaatagtgga 120  
ttgcggtant aaagattgtg cctgtctttt aaccacatca ggctengann gntctcgtga 180  
ac 182

<210> 413  
<211> 387  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (157)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (253)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (317)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (323)  
<223> n equals a,t,g, or c

<220>

<221> misc feature  
<222> (349)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (351)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (364)  
<223> n equals a,t,g, or c

<400> 413  
tcgacccacg cgtccgcca cgcgtccgcc aagaccacc tcctttcatt tgctagaagg 60  
actcactaga ctcaggaaag ctgttaggct cacagttaca gtttattaca gtaaaaggac 120  
agagattaag atcagcaaaag ggaggagggtg cacagcnacg ttccacgaca gatgaggcga 180  
cggcttccat ctgccctctc ccagtggagc catataggca gcacctgatt ctcacagcaa 240  
catgtgacaa canccaagaa gtactgcca tactgccaac cagagcagct tcactcggag 300  
atctttgtgt tccaganttt ttngttgtc ttggagacag ggtctgggnc ngtttgggca 360  
gacnaagagt acatggtgga gattcac 387

<210> 414  
<211> 276  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (60)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (186)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (195)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (237)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (260)



<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (266)

<223> n equals a,t,g, or c

<400> 414

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gcaaagggtcc atactgggta cttgggtttca ttgccaccac ttagtggtatg ttcagtttan 60
aaccattttg tctgctccct ctggaagcct tgcgcatagc ttactttgta attggtggag 120
aataactgct gaatttttag ctgttttgag ttgattcgca ccactgcacc acaactcact 180
atgaanacta tttancttat ttattatcct gtgaaaagta taccatgaaa attttgntca 240
tactgtattt atcaagtatn attaanagca ctagat 276
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<210> 415

<211> 192

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (78)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (99)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (145)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (150)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (164)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (168)  
<223> n equals a,t,g, or c

<400> 415  
aaaagattgg actaagacac tggccatacc actggacagg gttatgttaa cacctgaaat 60  
tgctgggtct tgagagancc caacgcantt ctgggagang gaccacattg ggggtaggt 120  
ccacgggctt ggtgatagaa ttatntctcn atcgacttct tgantgcnat atgaactgta 180  
acatttgctt ag 192

<210> 416  
<211> 439  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc feature  
<222> (7)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (9)  
<223> n equals a,t,g, or c

<220>  
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<222> (64)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (406)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (417)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (421)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature  
<222> (431)  
<223> n equals a,t,g, or c

<220>  
<221> misc feature

<222> (434)

<223> n equals a,t,g, or c

<400> 416

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gcgagantnc gacagaaggg tacggctgcg agagacgaca gaagggtacg gctgcgagaa 60
gacnacagaa ggggtacggct gcgagaagac gacagaaggg tacggctgcg agaagacgac 120
agaagggtac ggctgcgaga agacgacaga aggtacggct gcgagaagac gacagaagga 180
tacggctgcg agaagacgac agaagggaga atcttagttc aactttaaat ttgcccacag 240
aaccctctaa atccccttgt aaatttaact gttagtccaa agaggaacag ctctttggac 300
actaggaaaa aaccttgtag agagagttaa aaatttaaca cccatagtag gcctaaaagc 360
agccaccaat taagaaagcg ttcaaagctc aacacccact acccnaaaa taaaaanaaa 420
naaaaaccgc nggnccgct                                     439
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<210> 417

<211> 155

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (84)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (122)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (123)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (143)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (153)

<223> n equals a,t,g, or c

<400> 417

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gacatcttnt tggtttttat ttgaaacaa ttttaggct tgttccggg gtctctgtgc 60
tgctgtact gtattgacct gttntatagg tgccttttta taaaaagaa aattcaaaaa 120
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annaaaaaaaa aaattaataa aaaaaaaaa aanca

155

<210> 418

<211> 291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (286)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (288)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (291)

<223> n equals a,t,g, or c

<400> 418

gaaaaaagaa atccatatct taaagaaaca gctttcaagt gcctttctgc agtttttcag 60  
gagcgcaaga tagatttgga ataggaataa gctctagttc ttaacaaccg acactcctac 120  
aagatttaga aaaaagttta caacataatc tagtttacag aaaaatcttg tgctagaata 180  
cttttttaaaa ggtattttga ataccattaa aactgctttt ttttttcag caagtatcca 240  
accaacttgg ttctgcttca ataaatcttt ggaaaaacta atttnnanna n 291

<210> 419

<211> 340

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

&lt;222&gt; (315)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 419

Val Xaa Asp Trp Phe Leu Trp Tyr Val Lys Lys Cys Gly Gly Thr Thr  
 1 5 10 15

Arg Ile Ile Ser Thr Thr Asn Gly Gly Gln Glu Arg Lys Phe Val Gly  
 20 25 30

Gly Ser Gly Gln Val Ser Glu Arg Ile Met Asp Leu Leu Gly Asp Arg  
 35 40 45

Val Lys Leu Glu Arg Pro Val Ile Tyr Ile Asp Gln Thr Arg Glu Asn  
 50 55 60

Val Leu Val Glu Thr Leu Asn His Glu Met Tyr Glu Ala Lys Tyr Val  
 65 70 75 80

Ile Ser Ala Ile Pro Pro Thr Leu Gly Met Lys Ile His Phe Asn Pro  
 85 90 95

Pro Leu Pro Met Met Arg Asn Gln Met Ile Thr Arg Val Pro Leu Gly  
 100 105 110

Ser Val Ile Lys Cys Ile Val Tyr Tyr Lys Glu Pro Phe Trp Arg Lys  
 115 120 125

Lys Asp Tyr Cys Gly Thr Met Ile Ile Asp Gly Glu Glu Ala Pro Val  
 130 135 140

Ala Tyr Thr Leu Asp Asp Thr Lys Pro Glu Gly Asn Tyr Ala Ala Ile  
 145 150 155 160

Met Gly Phe Ile Leu Ala His Lys Ala Arg Lys Leu Ala Arg Leu Thr  
 165 170 175

Lys Glu Glu Arg Leu Lys Lys Leu Cys Glu Leu Tyr Ala Lys Val Leu  
 180 185 190

Gly Ser Leu Glu Ala Leu Glu Pro Val His Tyr Glu Glu Lys Asn Trp  
 195 200 205

Cys Glu Glu Gln Tyr Ser Gly Gly Cys Tyr Thr Thr Tyr Phe Pro Pro  
 210 215 220

Gly Ile Leu Thr Gln Tyr Gly Arg Val Leu Arg Gln Pro Val Asp Arg  
 225 230 235 240

Ile Tyr Phe Ala Gly Thr Glu Thr Ala Thr His Trp Ser Gly Tyr Met  
 245 250 255

368

Glu Gly Ala Val Glu Ala Gly Glu Arg Ala Ala Arg Glu Ile Leu His  
260 265 270  
Ala Met Gly Lys Ile Pro Glu Asp Glu Ile Trp Gln Ser Glu Pro Glu  
275 280 285  
Ser Val Asp Val Pro Ala Gln Pro Ile Thr Thr Thr Phe Leu Glu Arg  
290 295 300  
His Leu Pro Ser Val Pro Gly Leu Leu Arg Xaa Ile Gly Leu Thr Thr  
305 310 315 320  
Ile Phe Ser Ala Thr Ala Leu Gly Phe Leu Ala His Lys Arg Gly Leu  
325 330 335  
Leu Val Arg Val  
340

<210> 420  
<211> 111  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (48)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 420  
Thr Arg Asp Leu Val Ser Phe Ile Ser Gly Ile Arg Leu Tyr Asn Leu  
1 5 10 15  
Met Leu Ser Val Leu Arg His Lys Arg Gln Asn Val Ala Tyr Phe Arg  
20 25 30  
Ile Cys Phe Phe Ile Glu Val Ser Gly Ile Leu Ser Lys Ile Val Xaa  
35 40 45  
Ser Arg His Cys Ser Leu Cys Ser Ser Gly Thr Ser Cys Pro Leu Leu  
50 55 60  
Ser Leu Gln Ala Thr Gly Asn Ala Ser Val Leu Val Ser Trp Arg Lys  
65 70 75 80  
Ile Thr Trp Gly Glu Gly Thr Ser Cys Gly Lys Ser Lys Cys Arg Tyr  
85 90 95  
Glu Met Arg Arg Leu Pro Gln Leu Lys Val Asp Lys Ser Ala Leu

100

105

110

<210> 421  
 <211> 61  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 421  
 Xaa Ile Trp Cys Ile Ile Cys Lys Glu Ser Lys Met Met Ser Phe Pro  
           1                  5                  10                  15  
 Arg Gly Met Asn Leu Arg Asn Ala Phe Asp Gly Asp Val Ser Val Thr  
                   20                  25                  30  
 Leu Cys Tyr Ser Gly Ser Ser Asn Asn Ser Lys Ala Asn Tyr Ser Lys  
           35                  40                  45  
 Cys Lys Ile Phe Leu Phe Pro Arg Phe Thr Phe Val Trp  
           50                  55                  60

<210> 422  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 422  
 Thr His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp  
           1                  5                  10                  15  
 Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln His Arg Thr  
                   20                  25                  30  
 Arg Gly Ser Cys Pro Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro  
           35                  40                  45  
 Asp Lys Leu  
           50

<210> 423  
 <211> 246

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (101)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (117)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (147)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 423

Thr	Arg	Asn	Asp	Met	Lys	Ala	Asp	Cys	Ile	Leu	Tyr	Tyr	Gly	Phe	Gly
1				5					10					15	

Asp	Ile	Phe	Arg	Ile	Ser	Ser	Met	Val	Val	Met	Glu	Asn	Val	Gly	Gln
	20							25					30		

Gln	Lys	Leu	Tyr	Glu	Met	Val	Ser	Tyr	Cys	Gln	Asn	Ile	Ser	Lys	Cys
	35							40				45			

Arg	Arg	Val	Leu	Met	Ala	Gln	His	Phe	Asp	Glu	Val	Trp	Asn	Ser	Glu
	50					55					60				

Ala	Cys	Asn	Lys	Met	Cys	Xaa	Asn	Cys	Cys	Lys	Asp	Ser	Ala	Phe	Glu
65					70					75					80

Arg	Lys	Asn	Ile	Thr	Glu	Tyr	Cys	Arg	Asp	Leu	Ile	Lys	Ile	Leu	Lys
			85						90				95		

Gln	Ala	Glu	Gly	Xaa	Gly	Met	Glu	Lys	Leu	Thr	Pro	Ile	Gly	Asn	Trp
	100							105					110		

Ile	Asp	Ser	Trp	Xaa	Gly	Lys	Gly	Ala	Ala	Lys	Leu	Arg	Val	Ala	Gly
	115					120						125			

Val	Val	Ala	Pro	Thr	Leu	Pro	Arg	Glu	Asp	Leu	Glu	Lys	Ile	Ile	Ala
	130						135					140			



371

His Phe Xaa Ile Gln Gln Tyr Leu Lys Glu Asp Tyr Ser Phe Thr Ala  
 145 150 155 160

Tyr Ala Thr Ile Ser Tyr Leu Lys Ile Gly Pro Lys Ala Asn Leu Leu  
 165 170 175

Asn Asn Glu Ala His Ala Ile Thr Met Gln Val Thr Lys Ser Thr Gln  
 180 185 190

Asn Ser Phe Arg Ala Glu Ser Ser Gln Thr Cys His Ser Glu Gln Gly  
 195 200 205

Asp Lys Lys Met Glu Glu Lys Asn Ser Gly Asn Phe Gln Lys Lys Ala  
 210 215 220

Ala Asn Met Leu Gln Gln Ser Gly Ser Lys Asn Thr Gly Ala Lys Lys  
 225 230 235 240

Arg Lys Ile Asp Asp Ala  
 245

<210> 424

<211> 109

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 424

Asp His Trp Pro Arg Pro Glu Trp Leu Pro Cys Thr Ser Trp Arg Arg  
 1 5 10 15

Ala Ser Cys Leu Asn His Val Asn Cys His His Leu Ala Thr Pro Ala  
 20 25 30

Pro Ala Ser Ala Leu Pro Pro Phe Pro Pro Ser Trp Ser Gly Gly Tyr  
 35 40 45

Arg Ser Leu Gly Pro Thr Leu Ala Pro Leu Ser Pro Ala Ser Val Cys  
 50 55 60

Leu Thr Val Phe Pro Pro Leu Pro Gln Leu Arg Cys Xaa Pro Gln Ala  
 65 70 75 80

Trp Cys Cys Leu Gly Gly Leu Gly Glu Gly Val Cys Gly Gly Gly Arg  
 85 90 95

372

Arg Val Lys Thr Glu Ala Arg Cys Gln Asn Gly Leu Glu  
 100 105

&lt;210&gt; 425

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 425

Gly Ser Glu Thr Xaa Lys Tyr Leu Val Glu Asp Lys Arg Leu Gly Leu  
 1 5 10 15

Tyr Thr Trp Leu Cys Thr Asp Leu Leu Ser His Ile Gly Asn His His  
 20 25 30

Thr Leu Gln Gly Ile Ser Phe Ile Cys Lys Met Gln Arg Leu Val Leu  
 35 40 45

Xaa Asn His Thr Asn Phe Phe Val Leu  
 50 55

&lt;210&gt; 426

&lt;211&gt; 99

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (96)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 426

Phe Gly Thr Ser Gly Asp Gly Gly Gly Ser Lys Met Ala Gln Ala Ile  
 1 5 10 15

Phe Glu Ala Leu Glu Gly Met Asp Asn Gln Thr Val Leu Ala Val Gln

373

20                      25                      30  
 Ser Leu Leu Asp Gly Gln Gly Ala Val Pro Asp Pro Thr Gly Gln Ser  
      35                      40                      45  
 Val Asn Ala Pro Pro Ala Ile Gln Pro Leu Asp Asp Glu Asp Val Phe  
      50                      55                      60  
 Leu Cys Gly Lys Cys Lys Lys Gln Phe Asn Ser Leu Pro Ala Phe Met  
      65                      70                      75                      80  
 Thr His Lys Arg Glu Gln Cys Gln Gly Asn Ala Pro Ala Leu Ala Xaa  
              85                      90                      95

Val Ser Leu

&lt;210&gt; 427

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 427

Asn Ser Asn Ser Ser Ile Phe Ser Leu Val Ser Val Lys Cys Asp Lys  
      1                      5                      10                      15

Ser Thr Tyr Phe Lys Leu Phe Ser Ala Leu Gly Tyr Ser Ser Asn Lys  
              20                      25                      30

Asn Thr Asn Leu Trp Val Phe Lys Lys Thr Trp Arg Ile Asn Ser Tyr  
      35                      40                      45

Phe Lys Arg Ser Lys Lys Lys  
      50                      55

&lt;210&gt; 428

&lt;211&gt; 54

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 428

His Thr Leu Ser Asn Leu Glu Phe Ala Gln Lys Val Glu Pro Cys Asn

374

1                    5                    10                    15  
 Asp His Val Arg Ala Lys Leu Ser Trp Ala Lys Lys Arg Asp Glu Asp  
                   20                    25                    30  
 Asp Val Pro Thr Val Pro Ser Thr Xaa Gly Glu Glu Arg Leu Tyr Asn  
                   35                    40                    45  
 Pro Phe Leu Arg Val Ala  
                   50

<210> 429  
 <211> 39  
 <212> PRT  
 <213> Homo sapiens

<400> 429  
 Arg Gln Thr Lys Val Asn Leu Lys Glu Thr Arg Ser Phe Glu Ile Ile  
                   1                    5                    10                    15  
 Val Trp Gly Phe Tyr Lys Ser Asn Tyr Cys His Leu His Pro Asp Ser  
                   20                    25                    30  
 Phe Lys Leu Leu Ile His Pro  
                   35

<210> 430  
 <211> 133  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (81)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (85)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 430  
 Ala Arg Ala Pro Arg Val Pro Pro Ala Pro His Thr Pro Ser Lys Met  
                   1                    5                    10                    15  
 Gly Lys Glu Lys Thr His Ile Asn Ile Val Val Ile Gly His Val Asp  
                   20                    25                    30

375

Ser Gly Lys Ser Thr Thr Thr Gly His Leu Ile Tyr Lys Cys Gly Gly  
           35                    40                    45  
 Ile Asp Lys Arg Thr Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met  
           50                    55                    60  
 Gly Lys Gly Ser Phe Lys Tyr Ala Trp Val Leu Asp Lys Leu Lys Ala  
           65                    70                    75                    80  
 Xaa Val Ser Ala Xaa Ile Thr Ile Asp Ile Ser Leu Trp Lys Phe Glu  
                     85                    90                    95  
 Thr Thr Lys Tyr Tyr Ile Thr Ile Ile Asp Ala Pro Gly His Arg Asp  
           100                    105                    110  
 Phe Ile Lys Asn Met Ile Thr Gly Thr Ser Gln Ala Asp Cys Ala Val  
           115                    120                    125  
 Leu Ile Val Ala Ala  
           130

<210> 431  
 <211> 190  
 <212> PRT  
 <213> Homo sapiens

<400> 431  
 Leu Cys Trp Ala Arg Pro Leu Pro Ser Gly Pro Val Leu Leu Ala Ala  
           1                    5                    10                    15  
 Asn Lys Asp Ser Ser Trp Cys Pro Thr Cys Leu Val His Cys Cys Val  
           20                    25                    30  
 Asn Pro Gly Gly Ser Gly His Arg Arg Gln Pro Arg Pro Arg Val Gln  
           35                    40                    45  
 Glu Lys Cys Ser Leu Glu Ala Arg Thr Thr Ala Ser His Trp Gly Arg  
           50                    55                    60  
 Arg Gly Pro Arg Thr Thr Ser Ala Ser Tyr Leu Pro Ala Ser Ala Arg  
           65                    70                    75                    80  
 Gly Pro Arg Asp Ala Val Leu Phe Gln Pro Pro Ala Leu Gly Arg Gly  
           85                    90                    95  
 His Ala Ser Arg Ile Gln Gly Ala Gly Gly Leu Ser Thr Ala Arg Thr  
           100                    105                    110

376

Cys Leu Leu Ala Ala Ala Val Gly Glu His Gly Gly Cys Gln Arg  
 115 120 125  
 Leu Leu Trp Lys Val Ala Ala Ser Glu Met Ala Gly Ala Ala Gly Val  
 130 135 140  
 Arg Leu His Thr Ala Gln Val Ser Ser Gly Arg Leu Ser Trp Gly Gly  
 145 150 155 160  
 Ser Ser Ser Ala Glu Gly Trp Trp Gly Val Gln Ser Val Ile Leu Gly  
 165 170 175  
 Ala Val Cys Pro Thr Pro Ala Trp Gly Pro His Phe Arg Arg  
 180 185 190

<210> 432  
 <211> 310  
 <212> PRT  
 <213> Homo sapiens

<400> 432  
 Gly Pro His Gly Asn Gly Glu Val Arg Trp Pro Leu Pro Pro Pro  
 1 5 10 15  
 Pro Arg Phe Val Ala Arg Arg Lys Met Ala Asp Leu Glu Glu Gln Leu  
 20 25 30  
 Ser Asp Glu Glu Lys Val Arg Ile Ala Ala Lys Phe Ile Ile His Ala  
 35 40 45  
 Pro Pro Gly Glu Phe Asn Glu Val Phe Asn Asp Val Arg Leu Leu Leu  
 50 55 60  
 Asn Asn Asp Asn Leu Leu Arg Glu Gly Ala Ala His Ala Phe Ala Gln  
 65 70 75 80  
 Tyr Asn Leu Asp Gln Phe Thr Pro Val Lys Ile Glu Gly Tyr Glu Asp  
 85 90 95  
 Gln Val Leu Ile Thr Glu His Gly Asp Leu Gly Asn Gly Lys Phe Leu  
 100 105 110  
 Asp Pro Lys Asn Arg Ile Cys Phe Lys Phe Asp His Leu Arg Lys Glu  
 115 120 125  
 Ala Thr Asp Pro Arg Pro Cys Glu Val Glu Asn Ala Val Glu Ser Trp  
 130 135 140  
 Arg Thr Ser Val Glu Thr Ala Leu Arg Ala Tyr Val Lys Glu His Tyr

377

145                      150                      155                      160  
 Pro Asn Gly Val Cys Thr Val Tyr Gly Lys Lys Ile Asp Gly Gln Gln  
                                  165                      170                      175  
 Thr Ile Ile Ala Cys Ile Glu Ser His Gln Phe Gln Ala Lys Asn Phe  
                                  180                      185                      190  
 Trp Asn Gly Arg Trp Arg Ser Glu Trp Lys Phe Thr Ile Thr Pro Ser  
                                  195                      200                      205  
 Thr Thr Gln Val Val Gly Ile Leu Lys Ile Gln Val His Tyr Tyr Glu  
                                  210                      215                      220  
 Asp Gly Asn Val Gln Leu Val Ser His Lys Asp Ile Gln Asp Ser Leu  
 225                                   230                                   235                                   240  
 Thr Val Ser Asn Glu Val Gln Thr Ala Lys Glu Phe Ile Lys Ile Val  
                                  245                                   250                                   255  
 Glu Ala Ala Glu Asn Glu Tyr Gln Thr Ala Ile Ser Glu Asn Tyr Gln  
                                  260                                   265                                   270  
 Thr Met Ser Asp Thr Thr Phe Lys Ala Leu Arg Arg Gln Leu Pro Val  
                                  275                                   280                                   285  
 Thr Arg Thr Lys Ile Asp Trp Asn Lys Ile Leu Ser Tyr Lys Ile Gly  
                                  290                                   295                                   300  
 Lys Glu Met Gln Asn Ala  
 305                                   310

&lt;210&gt; 433

&lt;211&gt; 289

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (287)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (288)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 433

Gln Ser Cys Thr Ser Gly Ser Ser Lys Pro Asn Ser Pro Ser Ile Ser

378

1	5	10	15
Pro Ser Ile Leu Ser Asn Thr Glu His Lys Arg Gly Pro Glu Val Thr	20	25	30
Ser Gln Gly Val Gln Thr Ser Ser Pro Ala Cys Lys Gln Glu Lys Asp	35	40	45
Asp Lys Glu Glu Lys Lys Asp Ala Ala Glu Gln Val Arg Lys Ser Thr	50	55	60
Leu Asn Pro Asn Ala Lys Glu Phe Asn Pro Arg Ser Phe Ser Gln Pro	65	70	75
Lys Pro Ser Thr Thr Pro Thr Ser Pro Arg Pro Gln Ala Gln Pro Ser	85	90	95
Pro Ser Met Val Gly His Gln Gln Pro Thr Pro Val Tyr Thr Gln Pro	100	105	110
Val Cys Phe Ala Pro Asn Met Met Tyr Pro Val Pro Val Ser Pro Gly	115	120	125
Val Gln Pro Leu Tyr Pro Ile Pro Met Thr Pro Met Pro Val Asn Gln	130	135	140
Ala Lys Thr Tyr Arg Ala Gly Lys Val Pro Asn Met Pro Gln Gln Arg	145	150	155
Gln Asp Gln His His Gln Ser Ala Met Met His Pro Ala Ser Ala Ala	165	170	175
Gly Pro Pro Ile Ala Ala Thr Pro Pro Ala Tyr Ser Thr Gln Tyr Val	180	185	190
Ala Tyr Ser Pro Gln Gln Phe Pro Asn Gln Pro Leu Val Gln His Val	195	200	205
Pro His Tyr Gln Ser Gln His Pro His Val Tyr Ser Pro Val Ile Gln	210	215	220
Gly Asn Ala Arg Met Met Ala Pro Pro Thr His Ala Gln Pro Gly Leu	225	230	235
Val Ser Ser Ser Ala Thr Gln Tyr Gly Ala His Glu Gln Thr His Ala	245	250	255
Met Tyr Ala Cys Pro Lys Leu Pro Tyr Asn Lys Glu Thr Ser Pro Ser	260	265	270
Phe Tyr Phe Ala Ile Ser Thr Gly Ser Leu Ala Gln Gln Tyr Xaa Xaa			



379

275

280

285

Pro

&lt;210&gt; 434

&lt;211&gt; 147

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 434

Lys Val Thr Pro Asp Leu Lys Pro Thr Glu Ala Ser Ser Ser Ala Phe  
1 5 10 15

Arg Leu Met Pro Ala Leu Gly Val Ser Val Ala Asp Gln Lys Gly Lys  
20 25 30

Ser Thr Val Ala Ser Ser Glu Ala Lys Pro Ala Ala Thr Ile Arg Ile  
35 40 45

Val Gln Gly Leu Gly Val Met Pro Pro Lys Ala Gly Gln Thr Ile Thr  
50 55 60

Val Ala Thr His Ala Lys Gln Gly Ala Ser Val Ala Ser Gly Ser Gly  
65 70 75 80

Thr Val His Thr Ser Ala Val Ser Leu Pro Ser Met Asn Ala Ala Val  
85 90 95

Ser Lys Thr Val Ala Val Ala Ser Gly Ala Ala Arg Pro Pro Ser Ala  
100 105 110

Ser Ala Gln Glu Pro Pro Pro Cys Gly Arg Ser Leu Ser Ala Pro Arg  
115 120 125

Leu Cys Pro Arg Pro Arg Leu Gly Ser Cys Leu His Gly Ser Gln Phe  
130 135 140

Pro Ser Leu  
145

&lt;210&gt; 435

&lt;211&gt; 151

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

380

<221> SITE  
 <222> (9)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (15)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (79)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 435  
 Gly Ser Gly Thr Lys Asp Pro Ser Xaa Cys Asn Thr Gln Thr Xaa Ala  
   1                  5                  10                  15  
  
 His Thr His Thr Gly Gly Glu Ile Ser Leu Phe Ser Met Ser Phe Phe  
                   20                  25                  30  
  
 Ser Trp Ala Glu Thr Gly Tyr Cys Pro Gly Gln Leu Pro Glu Lys His  
           35                  40                  45  
  
 Arg Arg Glu Leu Arg Ser Ala Arg Pro Ser Ser Leu Ala Pro Gly Phe  
   50                  55                  60  
  
 Gly Gly Pro Arg Thr Ala Asp Arg Gly Trp Ser Trp Arg Leu Xaa Ser  
   65                  70                  75                  80  
  
 Arg Ala Tyr Thr Trp Arg Asn Ala Pro Pro Ser Ser Pro Ser Leu Gln  
                   85                  90                  95  
  
 Thr Trp Gly Trp Leu Gly Pro Glu Gly Cys Asp Glu Glu Lys Arg Ala  
           100                  105                  110  
  
 Ser Val Gly Met Arg Gln Glu Gly Ile Asp Phe Asp Cys Asp Leu Trp  
   115                  120                  125  
  
 Gly Phe Leu Pro Ala Leu Asp Asn Pro Ala Lys Asp Cys Phe Phe Leu  
   130                  135                  140  
  
 Ser Leu Ala Arg Arg Gly Pro  
   145                  150  
  
  
 <210> 436  
 <211> 180  
 <212> PRT  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (123)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 436

Ala	Pro	Ala	Ser	Pro	Val	Met	Pro	Pro	Gln	Thr	Gln	Ser	Pro	Gly	Gln
1				5					10					15	

Pro	Ala	Gln	Pro	Ala	Pro	Met	Val	Pro	Leu	His	Gln	Lys	Gln	Ser	Arg
		20						25					30		

Ile	Thr	Pro	Ile	Gln	Lys	Pro	Arg	Gly	Xaa	Asp	Pro	Val	Glu	Ile	Leu
		35					40					45			

Gln	Glu	Arg	Glu	Tyr	Arg	Leu	Gln	Ala	Arg	Ile	Ala	His	Arg	Ile	Gln
	50					55					60				

Glu	Leu	Glu	Asn	Leu	Pro	Gly	Ser	Leu	Ala	Gly	Asp	Leu	Arg	Thr	Lys
65					70					75				80	

Ala	Thr	Ile	Glu	Leu	Lys	Ala	Leu	Arg	Leu	Leu	Asn	Phe	Gln	Arg	Gln
				85					90					95	

Leu	Arg	Gln	Glu	Val	Val	Val	Cys	Met	Arg	Arg	Asp	Thr	Ala	Leu	Glu
		100						105					110		

Thr	Ala	Leu	Asn	Ala	Lys	Ala	Tyr	Lys	Arg	Xaa	Ser	Ala	Ser	Pro	Cys
		115					120					125			

Ala	Arg	Pro	Ala	Ser	Leu	Arg	Ser	Trp	Arg	Ser	Ser	Arg	Arg	Ser	Ser
	130					135					140				

Arg	Ser	Ala	Ser	Ala	Gly	Arg	Ser	Thr	Arg	Asn	Thr	Ser	Ile	Ala	Phe
145				150					155					160	

Ser	Ser	Met	Pro	Arg	Ile	Ser	Arg	Asn	Ile	Thr	Asp	Pro	Ser	Gln	Ala
			165						170					175	

Lys	Ser	Arg	Ser
			180

&lt;210&gt; 437

<211> 415  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (8)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (94)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (96)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (170)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 437  
 Arg Lys Tyr Leu Val Pro Leu Xaa Lys Lys Leu Tyr Leu Lys Trp Ala  
     1                    5                    10                    15  
 Leu Glu Glu Tyr Leu Asp Glu Phe Asp Pro Cys His Cys Arg Pro Cys  
                     20                    25                    30  
 Gln Asn Gly Gly Leu Ala Thr Val Glu Gly Thr His Cys Leu Cys His  
                     35                    40                    45  
 Cys Lys Pro Tyr Thr Phe Gly Ala Ala Cys Glu Gln Gly Val Leu Val  
     50                    55                    60  
 Gly Asn Gln Ala Gly Gly Val Asp Gly Gly Trp Ser Cys Trp Ser Ser  
     65                    70                    75                    80  
 Trp Ser Pro Cys Val Gln Gly Lys Lys Thr Arg Ser Arg Xaa Cys Xaa  
                     85                    90                    95  
 Asn Pro Pro Pro Ser Gly Gly Gly Arg Ser Cys Val Gly Glu Thr Thr  
                     100                    105                    110  
 Glu Ser Thr Gln Cys Glu Asp Glu Glu Leu Glu His Leu Arg Leu Leu  
     115                    120                    125  
 Glu Pro His Cys Phe Pro Leu Ser Leu Val Pro Thr Glu Phe Cys Pro  
     130                    135                    140

Ser Pro Pro Ala Leu Lys Asp Gly Phe Val Gln Asp Glu Gly Thr Met  
 145 150 155 160  
 Phe Pro Val Gly Lys Asn Val Val Tyr Xaa Cys Asn Glu Gly Tyr Ser  
 165 170 175  
 Leu Ile Gly Asn Pro Val Ala Arg Cys Gly Glu Asp Leu Arg Trp Leu  
 180 185 190  
 Val Gly Glu Met His Cys Gln Lys Ile Ala Cys Val Leu Pro Val Leu  
 195 200 205  
 Met Asp Gly Ile Gln Ser His Pro Gln Lys Pro Phe Tyr Thr Val Gly  
 210 215 220  
 Glu Lys Val Thr Val Ser Cys Ser Gly Gly Met Ser Leu Glu Gly Pro  
 225 230 235 240  
 Ser Ala Phe Leu Cys Gly Ser Ser Leu Lys Trp Ser Pro Glu Met Lys  
 245 250 255  
 Asn Ala Arg Cys Val Gln Lys Glu Asn Pro Leu Thr Gln Ala Val Pro  
 260 265 270  
 Lys Cys Gln Arg Trp Glu Lys Leu Gln Asn Ser Arg Cys Val Cys Lys  
 275 280 285  
 Met Pro Tyr Glu Cys Gly Pro Ser Leu Asp Val Cys Ala Gln Asp Glu  
 290 295 300  
 Arg Ser Lys Arg Ile Leu Pro Leu Thr Val Cys Lys Met His Val Leu  
 305 310 315 320  
 His Cys Gln Gly Arg Asn Tyr Thr Leu Thr Gly Arg Asp Ser Cys Thr  
 325 330 335  
 Leu Pro Ala Ser Ala Glu Lys Ala Cys Gly Ala Cys Pro Leu Trp Gly  
 340 345 350  
 Lys Cys Asp Ala Glu Ser Ser Lys Cys Val Cys Arg Glu Ala Ser Glu  
 355 360 365  
 Cys Glu Glu Glu Gly Phe Ser Ile Cys Val Glu Val Asn Gly Lys Glu  
 370 375 380  
 Gln Thr Met Ser Glu Cys Glu Ala Gly Ala Leu Arg Cys Arg Gly Gln  
 385 390 395 400  
 Ser Ile Ser Val Thr Ser Ile Arg Pro Cys Ala Ala Glu Thr Gln  
 405 410 415

<210> 438  
 <211> 285  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (16)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (17)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (18)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 438  
 Leu Ile Arg Leu Thr Ile Gly Lys Ala Gly Ser Leu Gln Tyr Arg Xaa  
   1                  5                  10                  15  
 Xaa Xaa Phe Pro Gly Met Glu Ala Phe Leu Gly Ser Arg Ser Gly Leu  
           20                  25                  30  
 Trp Ala Gly Gly Pro Ala Pro Gly Gln Phe Tyr Arg Ile Pro Ser Thr  
       35                  40                  45  
 Pro Asp Ser Phe Met Asp Pro Ala Ser Ala Leu Tyr Arg Gly Pro Ile  
       50                  55                  60  
 Thr Arg Thr Gln Asn Pro Met Val Thr Gly Thr Ser Val Leu Gly Val  
       65                  70                  75                  80  
 Lys Phe Glu Gly Gly Val Val Ile Ala Ala Asp Met Leu Gly Ser Tyr  
           85                  90                  95  
 Gly Ser Leu Ala Arg Phe Arg Asn Ile Ser Arg Ile Met Arg Val Asn  
       100                  105                  110  
 Asn Ser Thr Met Leu Gly Ala Ser Gly Asp Tyr Ala Asp Phe Gln Tyr  
       115                  120                  125  
 Leu Lys Gln Val Leu Gly Gln Met Val Ile Asp Glu Glu Leu Leu Gly  
       130                  135                  140

385

Asp Gly His Ser Tyr Ser Pro Arg Ala Ile His Ser Trp Leu Thr Arg  
145 150 155 160

Ala Met Tyr Ser Arg Arg Ser Lys Met Asn Pro Leu Trp Asn Thr Met  
165 170 175

Val Ile Gly Gly Tyr Ala Asp Gly Glu Ser Phe Leu Gly Tyr Val Asp  
180 185 190

Met Leu Gly Val Ala Tyr Glu Ala Pro Ser Leu Ala Thr Gly Tyr Gly  
195 200 205

Ala Tyr Leu Ala Gln Pro Leu Leu Arg Glu Val Leu Glu Lys Gln Pro  
210 215 220

Val Leu Ser Gln Thr Glu Ala Arg Asp Leu Val Glu Arg Cys Met Arg  
225 230 235 240

Val Leu Tyr Tyr Arg Asp Ala Arg Ser Tyr Asn Arg Phe Gln Ile Ala  
245 250 255

Thr Val Thr Glu Lys Gly Val Glu Ile Glu Gly Pro Leu Ser Thr Glu  
260 265 270

Thr Asn Trp Asp Ile Ala His Met Ile Ser Gly Phe Glu  
275 280 285

&lt;210&gt; 439

&lt;211&gt; 185

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 439

Asn Ser Ala Ala His Lys Lys Gly Lys Leu Pro Ile Val Asn Glu Asp  
1 5 10 15

Asp Glu Leu Val Ala Ile Ile Ala Arg Thr Asp Leu Lys Lys Asn Arg  
20 25 30

Asp Tyr Pro Leu Ala Ser Lys Asp Ala Lys Lys Gln Leu Leu Cys Gly  
35 40 45

Ala Ala Ile Gly Thr His Glu Asp Asp Lys Tyr Arg Leu Asp Leu Leu  
50 55 60

Ala Gln Ala Gly Val Asp Val Val Val Leu Asp Ser Ser Gln Gly Asn  
65 70 75 80

Ser Ile Phe Gln Ile Asn Met Ile Lys Tyr Ile Lys Asp Lys Tyr Pro

386

85	90	95
Asn Leu Gln Val Ile Gly Gly Asn Val Val Thr Ala Ala Gln Ala Lys		
100	105	110
Asn Leu Ile Asp Ala Gly Val Asp Ala Leu Arg Val Gly Met Gly Ser		
115	120	125
Gly Ser Ile Cys Ile Thr Gln Glu Val Leu Ala Cys Gly Arg Pro Gln		
130	135	140
Ala Thr Ala Val Tyr Lys Val Ser Glu Tyr Ala Arg Arg Phe Gly Val		
145	150	155
Pro Val Ile Ala Asp Gly Gly Ile Gln Asn Val Gly His Ile Ala Lys		
165	170	175
Ala Leu Ala Leu Gly Ala Pro Gln Ser		
180	185	

&lt;210&gt; 440

&lt;211&gt; 211

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 440

Leu Gln Gly Arg Ser Thr Pro Ile Trp Pro Ala Leu Ala Thr Val Thr		
1	5	10
Ser Arg Thr Pro Ala Leu Gly Pro Gln Ala Gly Ile Asp Thr Asn Glu		
20	25	30
Ile Ala Pro Leu Glu Pro Asp Ala Pro Pro Asp Ala Cys Glu Ala Ser		
35	40	45
Phe Asp Ala Val Ser Thr Ile Arg Gly Glu Leu Phe Phe Phe Lys Ala		
50	55	60
Gly Phe Val Trp Arg Leu Arg Gly Gly Gln Leu Gln Pro Gly Tyr Pro		
65	70	75
Ala Leu Ala Ser Arg His Trp Gln Gly Leu Pro Ser Pro Val Asp Ala		
85	90	95
Ala Phe Glu Asp Ala Gln Gly His Ile Trp Phe Phe Gln Gly Ala Gln		
100	105	110
Tyr Trp Val Tyr Asp Gly Glu Lys Pro Val Leu Gly Pro Ala Pro Leu		
115	120	125



387

Thr Glu Leu Gly Leu Val Arg Phe Pro Val His Ala Ala Leu Val Trp  
 130 135 140

Gly Pro Glu Lys Asn Lys Ile Tyr Phe Phe Arg Gly Arg Asp Tyr Trp  
 145 150 155 160

Arg Phe His Pro Ser Thr Arg Arg Val Asp Ser Pro Val Pro Arg Arg  
 165 170 175

Pro Leu Thr Gly Glu Gly Cys Pro Leu Arg Ser Thr Leu Pro Ser Arg  
 180 185 190

Met Leu Met Ala Met Pro Thr Ser Cys Ala Ala Ala Ser Thr Gly Ser  
 195 200 205

Leu Thr Leu  
 210

<210> 441

<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 441

Gly Gly Ala Gly Lys Leu Leu Ser Phe Thr His Ser Ala Pro Trp Ser  
 1 5 10 15

Arg Leu Trp Ser Ser Leu Gly Lys Arg Val Thr Gly Glu Ser Gln Gly  
 20 25 30

Leu Glu Lys Leu Pro Gly Thr Xaa Asp Gly Leu Ala Ala Leu Thr Gln  
 35 40 45

Asp Pro Leu Pro Leu Pro Pro Pro Leu Cys Arg Asn Thr Gly Thr Pro  
 50 55 60

Arg Gly Lys Met Ser Phe Ser Arg Leu Gln Phe Ser Pro Arg Lys Leu  
 65 70 75 80

<210> 442  
<211> 567  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (205)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (212)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (469)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (503)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (505)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (517)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (535)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (546)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 442  
Asn Val His Leu Tyr Ile Met Tyr Tyr Met Glu Ala Lys His Ala Val  
1 5 10 15

Ser Phe Met Thr Cys Thr Gln Asn Val Ala Pro Asp Met Phe Arg Thr

389

20	25	30
Ile Pro Pro Glu Ala Asn Ile Pro Ile Pro Val Lys Ser Asp Met Val		
35	40	45
Met Met His Glu His His Lys Glu Thr Glu Tyr Lys Asp Lys Ile Pro		
50	55	60
Leu Leu Gln Gln Pro Lys Arg Glu Glu Glu Glu Val Leu Asp Gln Gly		
65	70	75
Asp Phe Tyr Ser Leu Leu Ser Lys Leu Leu Gly Glu Arg Glu Asp Val		
85	90	95
Val His Val His Lys Tyr Asn Pro Thr Glu Lys Ala Glu Ser Glu Ser		
100	105	110
Asp Leu Val Ala Glu Ile Ala Asn Val Val Gln Lys Lys Asp Leu Gly		
115	120	125
Arg Ser Asp Ala Arg Glu Gly Ala Glu His Glu Arg Gly Asn Ala Ile		
130	135	140
Leu Val Arg Asp Arg Ile His Lys Phe His Arg Leu Val Ser Thr Leu		
145	150	155
Arg Pro Pro Glu Ser Arg Val Phe Ser Leu Gln Gln Pro Pro Pro Gly		
165	170	175
Glu Gly Thr Trp Glu Pro Glu His Thr Gly Asp Phe His Met Glu Glu		
180	185	190
Ala Leu Asp Trp Pro Gly Val Tyr Leu Leu Pro Gly Xaa Val Ser Gly		
195	200	205
Val Ala Leu Xaa Pro Lys Asn Asn Leu Val Ile Phe His Arg Gly Asp		
210	215	220
His Val Trp Asp Gly Asn Ser Phe Asp Ser Lys Phe Val Tyr Gln Gln		
225	230	235
Ile Gly Leu Gly Pro Ile Glu Glu Asp Thr Ile Leu Val Ile Asp Pro		
245	250	255
Asn Asn Ala Ala Val Leu Gln Ser Ser Gly Lys Asn Leu Phe Tyr Leu		
260	265	270
Pro His Gly Leu Ser Ile Asp Lys Asp Gly Asn Tyr Trp Val Thr Asp		
275	280	285
Val Ala Leu His Gln Val Phe Lys Leu Asp Pro Asn Asn Lys Glu Gly		

390

290	295	300
Pro Val Leu Ile Leu Gly Arg Ser Met Gln Pro Gly Ser Asp Gln Asn		
305	310	315 320
His Phe Cys Gln Pro Thr Asp Val Ala Val Asp Pro Gly Thr Gly Ala		
	325 330	335
Ile Tyr Val Ser Asp Gly Tyr Cys Asn Ser Arg Ile Val Gln Phe Ser		
	340 345	350
Pro Ser Gly Lys Phe Ile Thr Gln Trp Gly Glu Glu Ser Ser Gly Ser		
	355 360	365
Ser Pro Leu Pro Gly Gln Phe Thr Val Pro His Ser Leu Ala Leu Val		
	370 375	380
Pro Leu Leu Gly Gln Leu Cys Val Ala Asp Arg Glu Asn Gly Arg Ile		
385	390	395 400
Gln Cys Phe Lys Thr Asp Thr Lys Glu Phe Val Arg Glu Ile Lys His		
	405 410	415
Ser Ser Phe Gly Arg Asn Val Phe Ala Ile Ser Tyr Ile Pro Gly Leu		
	420 425	430
Leu Phe Ala Val Asn Gly Lys Pro His Phe Gly Asp Gln Glu Pro Val		
	435 440	445
Gln Gly Phe Val Met Asn Phe Ser Asn Gly Glu Ile Ile Asp Ile Phe		
	450 455	460
Lys Pro Val Arg Xaa Leu Leu Asp Met Pro His Asp Ile Val Ala Ser		
465	470	475 480
Glu Asp Gly Thr Val Tyr Ile Gly Arg Cys Ser Tyr Gln His Arg Val		
	485 490	495
Gly Ser Ser Thr Leu Asp Xaa Arg Xaa Leu Gly Thr Ser Val Gln Phe		
	500 505	510
Lys Lys Gly Leu Xaa Ile Glu Val Gln Gly Asn Pro Lys Lys Pro Glu		
	515 520	525
Gly Ile Cys Cys Phe Pro Xaa Thr Thr Leu Arg Val Ile Pro Val Val		
	530 535	540
Gly Xaa Trp Arg Gly His Gly Pro Asn Leu Ile Pro Val Gly Lys Asn		
545	550	555 560
Pro Arg Gly Pro Leu Gly Arg		

565

&lt;210&gt; 443

&lt;211&gt; 129

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (123)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (127)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (129)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 443

Arg	Pro	Ser	Cys	Ser	Pro	Gly	Ser	Val	Ser	Ala	Ala	Ala	Val	Asn	Met
1				5					10					15	

Glu	Pro	Pro	Asp	Ala	Pro	Ala	Gln	Ala	Arg	Gly	Ala	Pro	Arg	Leu	Leu
			20					25						30	

Leu	Leu	Ala	Val	Leu	Leu	Ala	Ala	His	Pro	Asp	Ala	Gln	Ala	Glu	Val
		35						40					45		

Arg	Leu	Ser	Val	Pro	Pro	Leu	Val	Glu	Val	Met	Arg	Gly	Lys	Ser	Val
	50					55					60				

Ile	Leu	Asp	Cys	Thr	Pro	Thr	Gly	Thr	His	Asp	His	Tyr	Met	Leu	Glu
65					70					75				80	

Trp	Phe	Leu	Thr	Asp	Arg	Ser	Gly	Ala	Arg	Pro	Arg	Leu	Ala	Ser	Ala
			85						90					95	

Glu	Met	Gln	Gly	Ser	Glu	Leu	Gln	Val	Thr	Met	His	Asp	Thr	Arg	Gly
		100						105					110		

Arg	Ser	Pro	Pro	Tyr	Gln	Leu	Gly	Leu	Pro	Xaa	Gly	Ala	Trp	Xaa	Leu
		115					120						125		

Xaa

392

<210> 444  
<211> 131  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 444

Glu Pro Arg Val Glu Arg Glu Thr Pro Gly Gln Pro Phe Ser Ser Ser  
1 5 10 15  
Phe Pro Ser Pro Ser Pro Phe Pro Asn Val Ala Ser Met Trp Val Leu  
20 25 30  
Gly Thr Trp Glu Lys Pro Leu Leu Cys His Phe Phe Ser Leu Phe Pro  
35 40 45  
Ser Ser Pro Pro Thr Val Trp Leu Met Met Ser Ser Gly Val Met Val  
50 55 60  
Thr Thr Pro Cys Ser Leu Phe Trp Tyr Phe Pro Cys Gln Phe Pro Leu  
65 70 75 80  
Ser Ala Arg Leu Cys Pro Lys Ile Pro Ser Ala Ser Ser Leu His Val  
85 90 95  
Ala Glu Gly Pro Gly Leu Pro Gln Val Pro Cys Leu Ser Asn Lys Val  
100 105 110  
Glu Thr Ile Lys Pro Gly Lys Lys Lys Gly Gly Arg Ser Lys Gly  
115 120 125  
Ser Pro Arg  
130

<210> 445  
<211> 405  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 445

Gly Thr Gly Leu Val Pro Ile Arg Gln Ser Thr Lys Phe Asp Ser Ser  
1 5 10 15  
Leu Asp Arg Lys Asp Lys Phe Ser Phe Asp Leu Gly Lys Gly Glu Val  
20 25 30  
Ile Lys Ala Trp Asp Ile Ala Ile Ala Thr Met Lys Val Gly Glu Val

393

35	40	45
Cys His Ile Thr Cys Lys Pro Glu Tyr Ala Tyr Gly Ser Ala Gly Ser		
50	55	60
Pro Pro Lys Ile Pro Pro Asn Ala Thr Leu Val Phe Glu Val Glu Leu		
65	70	75 80
Phe Glu Phe Lys Gly Glu Asp Leu Thr Glu Glu Glu Asp Gly Gly Ile		
85	90	95
Ile Arg Arg Ile Gln Thr Arg Gly Glu Gly Tyr Ala Lys Pro Asn Glu		
100	105	110
Gly Ala Ile Val Glu Val Ala Leu Glu Gly Tyr Tyr Lys Asp Lys Leu		
115	120	125
Phe Asp Gln Arg Glu Leu Arg Phe Glu Ile Gly Glu Gly Glu Asn Leu		
130	135	140
Asp Leu Pro Tyr Gly Leu Glu Arg Ala Ile Gln Arg Met Glu Lys Gly		
145	150	155 160
Glu His Ser Ile Val Tyr Leu Lys Pro Ser Tyr Ala Phe Gly Ser Val		
165	170	175
Gly Lys Glu Lys Phe Gln Ile Pro Pro Asn Ala Glu Leu Lys Tyr Glu		
180	185	190
Leu His Leu Lys Ser Phe Glu Lys Ala Lys Glu Ser Trp Glu Met Asn		
195	200	205
Ser Glu Glu Lys Leu Glu Gln Ser Thr Ile Val Lys Glu Arg Gly Thr		
210	215	220
Val Tyr Phe Lys Glu Gly Lys Tyr Lys Gln Ala Leu Leu Gln Tyr Lys		
225	230	235 240
Lys Ile Val Ser Trp Leu Glu Tyr Glu Ser Ser Phe Ser Asn Glu Glu		
245	250	255
Ala Gln Lys Ala Gln Ala Leu Arg Leu Ala Ser His Leu Asn Leu Ala		
260	265	270
Met Cys His Leu Lys Leu Gln Ala Phe Ser Ala Ala Ile Glu Ser Cys		
275	280	285
Asn Lys Ala Leu Glu Leu Asp Ser Asn Asn Glu Lys Gly Leu Phe Arg		
290	295	300
Arg Gly Glu Ala His Leu Ala Val Asn Asp Phe Glu Leu Ala Arg Ala		

394

305                      310                      315                      320  
 Asp Phe Gln Lys Val Leu Gln Leu Tyr Pro Asn Asn Lys Ala Ala Lys  
                                  325                      330                      335  
 Thr Gln Leu Ala Val Cys Gln Gln Arg Ile Arg Arg Gln Leu Ala Arg  
                                  340                      345                      350  
 Glu Lys Lys Leu Tyr Ala Asn Met Phe Glu Arg Leu Ala Glu Glu Glu  
                                  355                      360                      365  
 Asn Lys Ala Lys Ala Glu Ala Ser Ser Gly Asp His Pro Thr Asp Thr  
                                  370                      375                      380  
 Glu Met Lys Glu Glu Gln Lys Ser Asn Thr Ala Gly Ser Gln Ser Gln  
 385                                   390                      395                      400  
 Val Glu Thr Glu Ala  
                                  405

<210> 446  
 <211> 232  
 <212> PRT  
 <213> Homo sapiens

<400> 446  
 Pro Leu Val Pro Ser Ser Gln Lys Ala Leu Leu Leu Glu Leu Lys Gly  
   1                      5                      10                      15  
 Leu Gln Glu Glu Pro Val Glu Gly Phe Arg Val Thr Leu Val Asp Glu  
                                  20                      25                      30  
 Gly Asp Leu Tyr Asn Trp Glu Val Ala Ile Phe Gly Pro Pro Asn Thr  
                                  35                      40                      45  
 Tyr Tyr Glu Gly Gly Tyr Phe Lys Ala Arg Leu Lys Phe Pro Ile Asp  
                                  50                      55                      60  
 Tyr Pro Tyr Ser Pro Pro Ala Phe Arg Phe Leu Thr Lys Met Trp His  
                                  65                      70                      75                      80  
 Pro Asn Ile Tyr Glu Thr Gly Asp Val Cys Ile Ser Ile Leu His Pro  
                                  85                      90                      95  
 Pro Val Asp Asp Pro Gln Ser Gly Glu Leu Pro Ser Glu Arg Trp Asn  
                                  100                      105                      110  
 Pro Thr Gln Asn Val Arg Thr Ile Leu Leu Ser Val Ile Ser Leu Leu  
                                  115                      120                      125



Asn Glu Pro Asn Thr Phe Ser Pro Ala Asn Val Asp Ala Ser Val Met  
 130 135 140

Tyr Arg Lys Trp Lys Glu Ser Lys Gly Lys Asp Arg Glu Tyr Thr Asp  
 145 150 155 160

Ile Ile Arg Lys Gln Val Leu Gly Thr Arg Trp Thr Arg Val Asn Gly  
 165 170 175

Val Lys Val Pro Thr Thr Leu Ala Glu Tyr Cys Val Lys Thr Lys Ala  
 180 185 190

Pro Ala Pro Asp Glu Gly Ser Asp Leu Phe Tyr Asp Asp Tyr Tyr Glu  
 195 200 205

Asp Gly Glu Val Glu Glu Glu Ala Asp Ser Cys Phe Gly Asp Asp Glu  
 210 215 220

Asp Asp Ser Gly Thr Glu Glu Ser  
 225 230

<210> 447

<211> 356

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (191)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (263)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 447

Cys Ser Pro Pro Pro Pro Pro Ala Ala Ala Ala Xaa Ala Ala Ala Ala

396

1	5	10	15
Ala Met Ala Gln Tyr Lys Gly Ala Ala Ser Glu Ala Gly Arg Ala Met	20	25	30
His Leu Met Lys Lys Arg Glu Lys Gln Arg Glu Gln Met Glu Gln Met	35	40	45
Lys Gln Arg Ile Xaa Glu Glu Asn Ile Met Lys Ser Asn Ile Asp Lys	50	55	60
Lys Phe Ser Ala His Tyr Asp Ala Val Glu Ala Glu Leu Lys Ser Ser	65	70	75
Thr Val Gly Leu Val Thr Leu Asn Asp Met Lys Ala Lys Gln Glu Ala	85	90	95
Leu Val Lys Glu Arg Glu Lys Gln Leu Ala Lys Lys Glu Gln Ser Lys	100	105	110
Glu Leu Gln Met Lys Leu Glu Lys Leu Arg Glu Lys Glu Arg Lys Lys	115	120	125
Glu Ala Lys Arg Lys Ile Ser Ser Leu Ser Phe Thr Leu Glu Glu Glu	130	135	140
Glu Glu Gly Gly Glu Glu Glu Glu Ala Ala Met Tyr Glu Glu Glu	145	150	155
Met Glu Arg Glu Glu Ile Thr Thr Lys Lys Arg Lys Leu Gly Lys Asn	165	170	175
Pro Asp Val Asp Thr Ser Phe Leu Pro Asp Arg Asp Arg Glu Xaa Glu	180	185	190
Glu Asn Arg Leu Arg Glu Glu Leu Arg Gln Glu Trp Glu Ala Lys Gln	195	200	205
Glu Lys Ile Lys Ser Glu Glu Ile Glu Ile Thr Phe Ser Tyr Trp Asp	210	215	220
Gly Ser Gly His Arg Arg Thr Val Lys Met Arg Lys Gly Asn Thr Met	225	230	235
Gln Gln Phe Leu Gln Lys Ala Leu Glu Ile Leu Arg Lys Asp Phe Ser	245	250	255
Glu Leu Arg Ser Ala Gly Xaa Glu Gln Leu Met Tyr Ile Lys Glu Asp	260	265	270
Leu Ile Ile Pro His His His Ser Phe Tyr Asp Phe Ile Val Thr Lys			

397

275                      280                      285  
 Ala Arg Gly Lys Ser Gly Pro Leu Phe Asn Phe Asp Val His Asp Asp  
     290                      295                      300  
 Val Arg Leu Leu Ser Asp Ala Thr Val Glu Lys Asp Glu Ser His Ala  
     305                      310                      315                      320  
 Gly Lys Val Val Leu Arg Ser Trp Tyr Glu Lys Asn Lys His Ile Phe  
                     325                      330                      335  
 Pro Ala Ser Arg Trp Glu Pro Tyr Asp Pro Glu Lys Lys Trp Asp Lys  
                     340                      345                      350  
 Tyr Thr Ile Arg  
     355

<210> 448  
 <211> 88  
 <212> PRT  
 <213> Homo sapiens

<400> 448  
 Lys Thr His Lys Met Cys Asp Ala Phe Val Gly Thr Trp Lys Leu Val  
     1                      5                      10                      15  
 Ser Ser Glu Asn Phe Asp Asp Tyr Met Lys Glu Val Gly Val Gly Phe  
                     20                      25                      30  
 Ala Thr Arg Lys Val Ala Gly Met Ala Lys Pro Asn Met Ile Ile Ser  
                     35                      40                      45  
 Val Asn Gly Asp Val Ile Thr Ile Lys Ser Glu Ser Thr Phe Lys Asn  
     50                      55                      60  
 Thr Glu Ile Ser Phe Ile Leu Gly Gln Glu Phe Asp Glu Ala Leu Gln  
     65                      70                      75                      80  
 Met Thr Gly Lys Ser Arg Ala Pro  
                     85

<210> 449  
 <211> 171  
 <212> PRT  
 <213> Homo sapiens

<220>

398

&lt;221&gt; SITE

&lt;222&gt; (72)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (132)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 449

Leu Ile Leu Val Leu Met Phe Val Val Trp Met Lys Arg Arg Asp Lys  
 1 5 10 15

Glu Arg Gln Ala Lys Gln Leu Leu Ile Asp Pro Glu Asp Asp Val Arg  
 20 25 30

Asp Asn Ile Leu Lys Tyr Asp Glu Gly Gly Gly Glu Glu Asp Gln  
 35 40 45

Asp Tyr Asp Leu Ser Gln Leu Gln Gln Pro Asp Thr Val Glu Pro Asp  
 50 55 60

Ala Ile Lys Pro Val Gly Ile Xaa Arg Met Asp Glu Arg Pro Ile His  
 65 70 75 80

Ala Glu Pro Gln Tyr Pro Val Arg Ser Ala Ala Pro His Pro Gly Asp  
 85 90 95

Ile Gly Asp Phe Ile Asn Glu Gly Leu Lys Ala Ala Asp Asn Asp Pro  
 100 105 110

Thr Ala Pro Pro Tyr Asp Ser Leu Leu Val Phe Asp Tyr Glu Gly Ser  
 115 120 125

Gly Ser Thr Xaa Gly Ser Leu Ser Ser Leu Asn Ser Ser Ser Gly  
 130 135 140

Gly Glu Gln Asp Tyr Asp Tyr Leu Asn Asp Trp Gly Pro Arg Phe Lys  
 145 150 155 160

Lys Leu Ala Asp Met Tyr Gly Gly Gly Asp Asp  
 165 170

&lt;210&gt; 450

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 450

399

Lys Val Lys Ala Cys Cys Lys Asp Ile Phe Phe Leu Leu Leu Glu Gly  
 1 5 10 15

Asn Thr Lys Arg Lys Ile Ser Phe Phe His Gly Ala Phe Asp Asn Phe  
 20 25 30

Ser Leu

<210> 451

<211> 148

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (89)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 451

Arg Thr Leu His Pro Ala Thr Gly Pro Arg Ala Arg Pro Pro Arg Gly  
 1 5 10 15

Trp Arg Arg Arg Leu Cys Ala Gln Gly Pro Ala Pro Asp Trp Asp Pro  
 20 25 30

Gly Val Pro Pro Gly Leu Ala Ser Cys Gly Xaa Thr Val Trp Leu His  
 35 40 45

Phe Ser Asp Pro Ser Leu Gly Arg Lys Val Lys Glu Thr Gly Pro Ala  
 50 55 60

Ser Ala Phe Gly Leu Trp Phe Leu Asp Arg Val Leu Ser Pro Ser Pro  
 65 70 75 80

Pro Ser Ser Pro Asn Leu Ser His Xaa Arg Pro Leu Pro Ala Ala Pro  
 85 90 95

Ser Leu Leu Gly Ile Gly Ser Pro Glu Pro Pro Ser Pro Glu Pro Pro  
 100 105 110

Thr Pro Leu Pro Gly Pro Cys Gly Cys Trp Ala Ser His Leu Lys Glu  
 115 120 125

400

Gly Lys Val Val Gln Pro Glu Pro Val Glu Gln Cys Pro Val Trp Pro  
130 135 140

Pro Lys Pro Lys  
145

<210> 452

<211> 83

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (19)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (64)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 452

Asp Ser His Arg Pro Arg Ala Met Arg Ala Leu Trp Val Leu Gly Leu  
1 5 10 15

Ser Cys Xaa Leu Leu Thr Phe Gly Ser Val Arg Xaa Asp Asp Glu Val  
20 25 30

Asp Val Asp Gly Thr Val Glu Glu Asp Leu Gly Lys Ser Arg Glu Gly  
35 40 45

Ser Arg Thr Asp Asp Glu Val Val Gln Arg Glu Glu Glu Ala Ile Xaa  
50 55 60

Val Gly Trp Ile Lys Cys Ile Pro Asn Lys Arg Thr Xaa Glu Xaa Lys  
 65 70 75 80

Ser Arg Lys

<210> 453

<211> 240

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (234)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 453

Gly Trp Leu Pro Cys Gly Ser Ser Val Val Pro Ala Thr Pro Gly Ser  
 1 5 10 15

Pro Pro Ser Arg Phe Trp Leu Leu Pro Ala Met Ala Leu Arg Val Leu  
 20 25 30

Leu Leu Thr Ala Leu Thr Leu Cys His Gly Phe Asn Leu Asp Thr Glu  
 35 40 45

Asn Ala Met Thr Phe Gln Glu Asn Ala Arg Gly Phe Gly Gln Ser Val  
 50 55 60

Val Gln Leu Gln Gly Ser Arg Val Val Val Gly Ala Pro Gln Glu Ile  
 65 70 75 80

Val Ala Ala Asn Gln Arg Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr  
 85 90 95

Gly Ser Cys Glu Pro Ile His Leu Gln Val Pro Val Glu Ala Val Asn  
 100 105 110

Met Ser Leu Gly Leu Ser Leu Ala Ala Thr Thr Ser Pro Pro Gln Leu  
 115 120 125

Leu Ala Cys Gly Pro Thr Val His Gln Thr Cys Ser Glu Asn Thr Tyr  
 130 135 140

Val Lys Gly Leu Cys Phe Leu Phe Gly Ser Asn Leu Arg Gln Gln Pro  
 145 150 155 160

Gln Lys Phe Pro Glu Ala Leu Arg Gly Cys Pro Gln Glu Asp Ser Asp  
 165 170 175

402

Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His Asp Phe  
                   180                  185                  190

Arg Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu Lys Lys  
                   195                  200                  205

Ser Lys Thr Leu Phe Ser Leu Met Gln Tyr Ser Glu Glu Phe Arg Ile  
                   210                  215                  220

His Phe Thr Ser Lys Ser Ser Arg Thr Xaa Leu Thr Gln Asp His Trp  
                   225                  230                  235                  240

&lt;210&gt; 454

&lt;211&gt; 244

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (206)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (227)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (229)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (239)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 454

Lys Trp Cys Ser Trp Thr Leu Leu Lys Ile Trp Glu Val Thr Cys Thr  
           1                  5                  10                  15

Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu Gly Gln Met  
           20                  25                  30

Ile Asn Leu Arg Arg Leu Leu Leu Ser His Ile His Ala Ser Ser Tyr



403

35                      40                      45  
 Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe Thr Ser Gln  
 50                      55                      60  
 Phe Leu Ser Leu Gln Cys Leu Gln Leu Leu Tyr Val Asp Ser Leu Phe  
 65                      70                      75                      80  
 Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val Met Asn Pro  
 85                      90                      95  
 Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu Gly Asp Val  
 100                      105                      110  
 Met His Leu Ser Gln Ser Pro Ser Val Ser Gln Leu Ser Val Leu Ser  
 115                      120                      125  
 Leu Ser Gly Val Met Leu Thr Asp Val Ser Pro Glu Pro Leu Gln Ala  
 130                      135                      140  
 Leu Leu Glu Arg Ala Ser Ala Thr Leu Gln Asp Leu Val Phe Asp Glu  
 145                      150                      155                      160  
 Cys Gly Ile Thr Asp Asp Gln Leu Leu Ala Leu Leu Pro Ser Leu Ser  
 165                      170                      175  
 His Cys Ser Gln Leu Thr Thr Leu Ser Phe Tyr Gly Asn Ser Ile Ser  
 180                      185                      190  
 Ile Ser Ala Leu Gln Ser Leu Leu Gln His Leu Ile Gly Xaa Ser Asn  
 195                      200                      205  
 Leu Thr His Val Leu Tyr Pro Val Pro Leu Glu Ser Tyr Glu Asp Ile  
 210                      215                      220  
 His Gly Xaa Leu Xaa Leu Glu Arg Leu Leu Ser Ala Cys Gln Xaa Gln  
 225                      230                      235                      240  
 Gly Val Ala Val

&lt;210&gt; 455

&lt;211&gt; 195

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 455

His Glu Gly Thr Gln Ser Phe Val Phe Gln Arg Glu Glu Ile Ala Gln  
 1                      5                      10                      15

404

Leu Ala Arg Gln Tyr Ala Gly Leu Asp His Glu Leu Ala Phe Ser Arg  
 20 25 30

Leu Ile Val Glu Leu Arg Arg Leu His Pro Gly His Val Leu Pro Asp  
 35 40 45

Glu Glu Leu Gln Trp Val Phe Val Asn Ala Gly Gly Trp Met Gly Ala  
 50 55 60

Met Cys Leu Leu His Ala Ser Leu Ser Glu Tyr Val Leu Leu Phe Gly  
 65 70 75 80

Thr Ala Leu Gly Ser Arg Gly His Ser Gly Arg Tyr Trp Ala Glu Ile  
 85 90 95

Ser Asp Thr Ile Ile Ser Gly Thr Phe His Gln Trp Arg Glu Gly Thr  
 100 105 110

Thr Lys Ser Glu Val Phe Tyr Pro Gly Glu Thr Val Val His Gly Pro  
 115 120 125

Gly Glu Ala Thr Ala Val Glu Trp Gly Pro Asn Thr Trp Met Val Glu  
 130 135 140

Tyr Gly Arg Gly Val Ile Pro Ser Thr Leu Ala Phe Ala Leu Ala Asp  
 145 150 155 160

Thr Val Phe Ser Thr Gln Asp Phe Leu Thr Leu Phe Tyr Thr Leu Arg  
 165 170 175

Ser Tyr Ala Arg Gly Leu Arg Leu Glu Leu Thr Thr Tyr Leu Phe Gly  
 180 185 190

Gln Asp Pro  
 195

<210> 456

<211> 36

<212> PRT

<213> Homo sapiens

<400> 456

Leu Val Thr Leu Leu His Ala Met Gln Ala Arg Asp Lys Thr Leu Gly  
 1 5 10 15

Leu Ala Thr Leu Cys Ile Gly Gly Gly Gln Gly Ile Ala Met Val Ile  
 20 25 30

Glu Arg Leu Asn  
35

<210> 457

<211> 152

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (86)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (114)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 457

Val Thr Ala Ala Ala Ser Val Arg Ala Leu Gln Val Thr Val Ala Gly  
1 5 10 15

Leu Leu Leu Val Phe Phe Leu Phe Gly Ala Pro Leu Asp Ser Leu Pro  
20 25 30

Ser Met Lys Ala Leu Ser Pro Val Arg Gly Cys Tyr Glu Ala Val Cys  
35 40 45

Cys Leu Ser Glu Arg Ser Leu Ala Ile Ala Arg Gly Arg Gly Lys Gly  
50 55 60

Pro Ala Ala Glu Glu Pro Leu Ser Leu Leu Asp Asp Met Asn His Cys  
65 70 75 80

Tyr Ser Arg Leu Arg Xaa Leu Val Pro Gly Val Pro Arg Gly Thr Gln  
85 90 95

Leu Ser Gln Val Glu Ile Leu Gln Arg Val Ile Asp Tyr Ile Leu Asp  
100 105 110

Leu Xaa Val Val Leu Ala Glu Pro Ala Pro Gly Pro Pro Asp Gly Pro  
115 120 125

His Leu Pro Ile Gln Thr Ala Glu Leu Ala Pro Glu Leu Val Ile Ser  
130 135 140

Asn Asp Lys Arg Ser Phe Cys His  
145 150

<210> 458  
<211> 31  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (17)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (25)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (31)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 458  
Leu Leu Asn Asn Phe Ile Phe Leu Glu Thr His Tyr Leu Trp Ala Cys  
1 5 10 15

Xaa Thr Trp Thr Ile Trp Pro Asn Xaa Leu Asp Lys Lys Gly Xaa  
20 25 30

<210> 459  
<211> 157  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (28)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (72)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (124)  
<223> Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (130)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 459

Asp Pro Arg Val Arg Glu Thr Thr Val Lys Ala Arg Ala Arg Ser Gln  
 1 5 10 15

His Ala Gly Gly Pro Glu Leu Gly Leu Ser Gln Xaa Tyr Val Thr Pro  
 20 25 30

Arg Arg Pro Phe Glu Lys Ser Arg Leu Asp Gln Glu Leu Lys Leu Ile  
 35 40 45

Gly Glu Tyr Gly Leu Arg Asn Lys Arg Glu Val Trp Arg Val Lys Phe  
 50 55 60

Thr Leu Ala Lys Ile Arg Lys Xaa Ala Arg Glu Leu Leu Thr Leu Asp  
 65 70 75 80

Glu Lys Asp Pro Arg Arg Leu Phe Glu Gly Asn Ala Leu Leu Arg Arg  
 85 90 95

Leu Val Arg Ile Gly Val Leu Asp Glu Gly Lys Met Lys Leu Asp Tyr  
 100 105 110

Ile Leu Gly Leu Lys Met Arg Ile Leu Gly Glu Xaa Ser Ala Asp Pro  
 115 120 125

Gly Xaa Ser Ser Trp Gly Trp Pro Ile His Pro Pro Cys Pro Val Leu  
 130 135 140

Ile Arg Gln Ala Thr Gln Val Arg Lys Gln Val Val Asn  
 145 150 155

&lt;210&gt; 460

&lt;211&gt; 136

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (119)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (130)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 460

Ile Trp Ala Pro Phe Pro His His Gln Gly Ser Gly Ser Gln Val Ser  
1 5 10 15

Ser Tyr Gly Thr Gly Ala Leu Lys Ser His Ile Met Ala Ala Lys Ala  
20 25 30

Val Ala Asn Thr Met Arg Thr Ser Leu Gly Pro Asn Gly Leu Asp Lys  
35 40 45

Met Met Val Asp Lys Asp Gly Asp Val Thr Val Thr Asn Asp Gly Ala  
50 55 60

Thr Ile Leu Ser Met Met Asp Val Asp His Gln Ile Ala Lys Leu Met  
65 70 75 80

Val Glu Leu Ser Lys Ser Gln Asp Asp Glu Ile Gly Asp Gly Asp His  
85 90 95

Gly Gly Gly Cys Pro Gly Arg Arg Pro Ala Gly Arg Arg Pro Ser Ser  
100 105 110

Cys Trp Thr Ala Ala Phe Xaa Arg Ser Gly Ser Pro Thr Val Thr Ser  
115 120 125

Arg Xaa Pro Ala Leu Ala Xaa Glu  
130 135

<210> 461

<211> 390

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (375)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (382)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (383)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (386)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (387)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 461  
 Cys Gly Asn Trp Trp Val Pro Arg Ala Gly Xaa Asn Trp Xaa Arg Gly  
   1                  5                  10                  15  
 Ser Arg Phe Leu Phe Val Asp Arg Cys Asp Arg His Leu Thr Met Gln  
           20                  25                  30  
 Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu  
       35                  40                  45  
 Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu  
       50                  55                  60  
 Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu  
   65                  70                  75                  80  
 Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr  
           85                  90                  95  
 Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys  
       100                  105                  110  
 Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr  
   115                  120                  125

Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro  
 130 135 140  
 Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg  
 145 150 155 160  
 Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val  
 165 170 175  
 Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly  
 180 185 190  
 Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val  
 195 200 205  
 Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg  
 210 215 220  
 Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp  
 225 230 235 240  
 Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg  
 245 250 255  
 Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr  
 260 265 270  
 Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile  
 275 280 285  
 Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala  
 290 295 300  
 Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln  
 305 310 315 320  
 Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln  
 325 330 335  
 Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu  
 340 345 350  
 Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Arg Ser Arg Gln Gly Arg  
 355 360 365  
 His Pro Pro Asp Gln Gln Xaa Leu Ile Leu Leu Gly Lys Xaa Xaa Lys  
 370 375 380  
 Trp Xaa Xaa Pro Phe Asp  
 385 390



411

<210> 462  
 <211> 171  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (74)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (135)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (142)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (155)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 462  
 Cys Ser Thr Val Arg Ile Pro Gly Ser Thr His Ala Ser Gly Leu Ser  
   1                  5                  10                  15  
 Arg Arg Ala Ser Pro Val Tyr Leu Ala Ser Met Ser Gly Arg Gly Lys  
           20                  25                  30  
 Thr Gly Gly Lys Ala Arg Ala Lys Ala Lys Ser Arg Ser Ser Arg Ala  
           35                  40                  45  
 Gly Leu Gln Phe Pro Val Gly Arg Val His Arg Leu Leu Arg Lys Gly  
   50                  55                  60  
 His Tyr Ala Glu Arg Val Gly Ala Gly Xaa Pro Val Tyr Leu Ala Ala  
   65                  70                  75                  80  
 Val Leu Glu Tyr Leu Thr Ala Glu Ile Leu Glu Leu Ala Gly Asn Ala  
           85                  90                  95  
 Ala Arg Asp Asn Lys Lys Thr Arg Ile Ile Pro Arg His Leu Gln Leu  
          100                 105                 110  
 Ala Ile Arg Asn Asp Glu Glu Leu Asn Lys Leu Leu Gly Gly Val Thr  
          115                 120                 125

412

Ile Ala Gln Gly Arg Arg Xaa Ala Gln His Pro Gly Arg Xaa Cys Cys  
 130 135 140

Pro Arg Arg Pro Ala Pro Pro Trp Gly Arg Xaa Pro Phe Gly Gly Gln  
 145 150 155 160

Glu Arg Ala Thr Lys Ala Ser Gln Gly Val Leu  
 165 170

&lt;210&gt; 463

&lt;211&gt; 433

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 463

Arg Val Arg Ala Pro Pro Arg Pro Pro Leu Gly Pro Ser Arg Pro Ser  
 1 5 10 15

His His Val His Pro Leu Gln Leu Pro Gly Ile Arg Glu Val Thr Ile  
 20 25 30

Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala Asp Pro Ser Leu  
 35 40 45

Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys Thr Leu Asn Asn  
 50 55 60

Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu Glu Gln Gln Asn  
 65 70 75 80

Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu Gln Lys Ser Ala  
 85 90 95

Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln Ile Ala Gly Leu  
 100 105 110

Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly Arg Leu Glu Ala  
 115 120 125

Glu Leu Arg Ser Met Gln Asp Val Val Glu Asp Phe Lys Asn Lys Tyr  
 130 135 140

Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn Glu Phe Val Val  
 145 150 155 160

Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys Val Glu Leu Glu  
 165 170 175

Ala Lys Val Asp Ala Leu Asn Asp Glu Ile Asn Phe Leu Arg Thr Leu  
 180 185 190  
 Asn Glu Thr Glu Leu Thr Glu Leu Gln Ser Gln Ile Ser Asp Thr Ser  
 195 200 205  
 Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Leu Asp Gly Ile  
 210 215 220  
 Ile Ala Glu Val Lys Ala Gln Tyr Glu Glu Met Ala Lys Cys Ser Arg  
 225 230 235 240  
 Ala Glu Ala Glu Ala Trp Tyr Gln Thr Lys Phe Glu Thr Leu Gln Ala  
 245 250 255  
 Gln Ala Gly Lys His Gly Asp Asp Leu Arg Asn Thr Arg Asn Glu Ile  
 260 265 270  
 Ser Glu Met Asn Arg Ala Ile Gln Arg Leu Gln Ala Glu Ile Asp Asn  
 275 280 285  
 Ile Lys Asn Gln Arg Ala Lys Leu Glu Ala Ala Ile Ala Glu Ala Glu  
 290 295 300  
 Glu Arg Gly Glu Leu Ala Leu Lys Asp Ala Arg Ala Lys Gln Glu Glu  
 305 310 315 320  
 Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala Arg Gln Leu  
 325 330 335  
 Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala Leu Asp Ile Glu  
 340 345 350  
 Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser Arg Leu Ala  
 355 360 365  
 Gly Asp Gly Val Gly Ala Val Asn Ile Ser Val Met Asn Ser Thr Gly  
 370 375 380  
 Gly Ser Ser Ser Gly Gly Gly Ile Gly Leu Thr Leu Gly Gly Thr Met  
 385 390 395 400  
 Gly Ser Asn Ala Leu Ser Phe Ser Ser Ser Ala Gly Pro Gly Leu Leu  
 405 410 415  
 Lys Ala Tyr Ser Ile Arg Thr Ala Ser Ala Ser Arg Arg Ser Ala Arg  
 420 425 430

Asp

<210> 464  
<211> 121  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (50)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (64)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (110)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (114)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (115)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (117)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 464  
Gly Ser Gly Cys Val Phe Ala Ile Leu Gly Arg Arg Cys Ser Arg Pro  
1 5 10 15  
Trp Arg Ile Trp Pro Gly Glu Pro Leu Gln Arg Ala Pro Pro Ala Ala  
20 25 30  
Gly Thr Arg Trp Pro His Gly His Arg Ser Ser Pro Val Gly Thr Pro  
35 40 45  
Gly Xaa Ala Pro Asn Val Pro Ala Ile Trp Gln Gln Pro Leu Trp Xaa  
50 55 60  
Glu Tyr Ser Cys Glu Tyr Gly Ser Met Lys Phe Tyr Ala Leu Cys Gly

415

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<400> 465
Arg Ile Pro Ala Pro Ala Ser Ser Arg His Ser Gly Gly Arg Cys Ala
 1             5             10             15
Ala Gly Pro Arg Gly Pro Pro Ala Thr Ala Ser Arg Ala Leu Arg Ala
          20             25             30
Val His Arg Pro Leu Asp Ala Ala Arg Gly Arg Thr Gly Ser Thr Ser
          35             40             45
His Leu Cys Ser Ser Ser Tyr Thr Ile Gly Cys Leu Leu Trp Phe Ser
 50             55             60
Gln Lys Ala Met
 65

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<400> 466

Ala Thr Ile Leu Glu Arg Glu Ala Glu Gln Ser Arg Leu Gly Ala Thr  
1 5 10 15

Glu Arg Ala Ala Ala Ala Ala Met Asn Pro Glu Tyr Asp Tyr Leu Phe  
20 25 30

Lys Leu Leu Leu Ile Gly Asp Ser Gly Val Gly Lys Ser Cys Leu Leu  
35 40 45

416

Leu Arg Phe Ala Asp Asp Thr Tyr Thr Glu Ser Tyr Ile Ser Thr Ile  
 50 55 60  
 Gly Val Asp Phe Lys Ile Arg Thr Ile Glu Leu Asp Gly Lys Thr Ile  
 65 70 75 80  
 Lys Leu Gln Ile Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Thr Ile  
 85 90 95  
 Thr Ser Ser Tyr Tyr Arg Gly Ala His Gly Ile Ile Val Val Tyr Asp  
 100 105 110  
 Val Thr Asp Gln Glu Ser Tyr Ala Asn Val Lys Gln Trp Leu Gln Glu  
 115 120 125  
 Ile Asp Arg Tyr Ala Ser Glu Asn Val Asn Lys Leu Leu Val Gly Asn  
 130 135 140  
 Lys Ser Asp Leu Thr Thr Lys Lys Val Val Asp Asn Thr Thr Ala Lys  
 145 150 155 160  
 Glu Phe Ala Asp Ser Leu Gly Ile Pro Phe Leu Glu Thr Ser Ala Lys  
 165 170 175  
 Asn Ala Thr Asn Val Glu Gln Ala Phe Met Thr Met Ala Ala Glu Ile  
 180 185 190  
 Lys Lys Arg Met Gly Pro Gly Ala Ala Ser Gly Gly Glu Arg Pro Asn  
 195 200 205  
 Leu Lys Ile Asp Ser Thr Pro Val Lys Pro Ala Gly Gly Gly Cys Cys  
 210 215 220

<210> 467  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 467

Ser Glu Ala Pro Gly Glu Ser Val Gly Thr Thr Pro Glu Ala Gln Met  
 1 5 10 15

Lys Thr Gly Pro Phe Ala Glu His Ser Asn Gln Leu Trp Asn Ile Ser  
 20 25 30

Ala Val Pro Ser Trp Ser Lys Val Asn Gln Gly Leu Ile Arg Met Tyr

417

35 40 45  
Lys Ala Glu Cys Leu Glu Lys Phe Pro Val Ile Gln His Phe Lys Phe  
50 55 60

Gly Ser Leu Leu Pro Ile His Pro Val Thr Ser Gly  
65 70 75

&lt;210&gt; 468

&lt;211&gt; 111

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (78)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (97)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 468

Ser Leu Ala Arg Thr Gly Pro Arg Ser Leu Ala Arg Pro Cys Arg Arg  
1 5 10 15

Arg Pro Ala His Arg His Pro Leu Gln Pro Cys Pro Pro Gly Xaa Cys  
20 25 30

Pro Arg Xaa Pro Thr Ala Asp Val Arg Arg Pro Arg His Arg Xaa Arg  
           35                    40                    45

Xaa Glu Leu His Ala His Asn Val Thr Ser Pro Pro Ala Pro Thr Ala  
           50                    55                    60

Trp Ala Ala Pro Ala Pro Gln His Gln Pro Gln Pro Leu Xaa Leu Val  
           65                    70                    75                    80

Pro Gly Arg Arg Val Cys Ser Arg Leu Leu Pro Arg Cys Ala Cys Gly  
                     85                    90                    95

Xaa Cys Cys Pro Gly Val Ala Leu Ala Gly Arg Ile Pro Trp Asn  
                     100                    105                    110

&lt;210&gt; 469

&lt;211&gt; 459

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 469

Pro Arg Val Arg Pro Arg Val Arg Pro Arg Val Arg Leu Ser Ser Pro  
   1                    5                    10                    15

Ser Pro Val Cys Leu Pro Pro Ala Ala Ala Thr Met Thr Thr Ser Ile  
           20                    25                    30

Arg Gln Phe Thr Ser Ser Ser Ser Ile Lys Gly Ser Ser Gly Leu Gly  
           35                    40                    45

Gly Gly Ser Ser Arg Thr Ser Cys Arg Leu Ser Gly Gly Leu Gly Ala  
           50                    55                    60

Gly Ser Cys Arg Leu Gly Ser Ala Gly Gly Leu Gly Ser Thr Leu Gly  
           65                    70                    75                    80

Gly Ser Ser Tyr Ser Ser Cys Tyr Ser Phe Gly Ser Gly Gly Gly Tyr  
                     85                    90                    95

Gly Ser Ser Phe Gly Gly Val Asp Gly Leu Leu Ala Gly Gly Glu Lys  
           100                    105                    110

Ala Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp Lys  
           115                    120                    125

Val Arg Ala Leu Glu Glu Ala Asn Thr Glu Leu Glu Val Lys Ile Arg  
           130                    135                    140



Asp Trp Tyr Gln Arg Gln Ala Pro Gly Pro Ala Arg Asp Tyr Ser Gln  
 145 150 155 160  
 Tyr Tyr Arg Thr Ile Glu Glu Leu Gln Asn Lys Ile Leu Thr Ala Thr  
 165 170 175  
 Val Asp Asn Ala Asn Ile Leu Leu Gln Ile Asp Asn Ala Arg Leu Ala  
 180 185 190  
 Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg Leu  
 195 200 205  
 Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu Leu  
 210 215 220  
 Thr Leu Ala Arg Ala Asp Leu Glu Met Gln Ile Glu Asn Leu Lys Glu  
 225 230 235 240  
 Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Met Asn Ala Leu  
 245 250 255  
 Arg Gly Gln Val Gly Gly Glu Ile Asn Val Glu Met Asp Ala Ala Pro  
 260 265 270  
 Gly Val Asp Leu Ser Arg Ile Leu Asn Glu Met Arg Asp Gln Tyr Glu  
 275 280 285  
 Lys Met Ala Glu Lys Asn Arg Lys Asp Ala Glu Asp Trp Phe Phe Ser  
 290 295 300  
 Lys Thr Glu Glu Leu Asn Arg Glu Val Ala Thr Asn Ser Glu Leu Val  
 305 310 315 320  
 Gln Ser Gly Lys Ser Glu Ile Ser Glu Leu Arg Arg Thr Met Gln Ala  
 325 330 335  
 Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ser Leu Glu  
 340 345 350  
 Gly Asn Leu Ala Glu Thr Glu Asn Arg Tyr Cys Val Gln Leu Ser Gln  
 355 360 365  
 Ile Gln Gly Leu Ile Gly Ser Val Glu Glu Gln Leu Ala Gln Leu Arg  
 370 375 380  
 Cys Glu Met Glu Gln Gln Asn Gln Glu Tyr Lys Ile Leu Leu Asp Val  
 385 390 395 400  
 Lys Thr Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu  
 405 410 415

420

Gly Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr  
 420 425 430

Arg Gln Val Arg Thr Ile Val Glu Glu Val Gln Asp Gly Lys Val Ile  
 435 440 445

Ser Ser Arg Glu Gln Val His Gln Thr Thr Arg  
 450 455

&lt;210&gt; 470

&lt;211&gt; 158

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (158)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 470

Pro Pro Pro Pro Pro Pro Pro Glu Leu Cys Ser Met Ala Ser Arg Arg  
 1 5 10 15

Met Glu Thr Lys Pro Val Ile Thr Cys Leu Lys Thr Leu Leu Ile Ile  
 20 25 30

Tyr Ser Phe Val Phe Trp Ile Thr Gly Val Ile Leu Leu Ala Val Gly  
 35 40 45

Val Trp Gly Lys Leu Thr Leu Gly Thr Tyr Ile Ser Leu Ile Ala Glu  
 50 55 60

Asn Ser Thr Asn Ala Pro Tyr Val Leu Ile Gly Thr Gly Thr Thr Ile  
 65 70 75 80

Val Val Phe Gly Leu Phe Gly Cys Phe Ala Thr Cys Arg Gly Ser Pro  
 85 90 95

Trp Met Leu Lys Leu Tyr Ala Met Phe Leu Ser Leu Val Phe Leu Ala  
 100 105 110

Glu Leu Val Ala Gly Ile Ser Gly Phe Val Phe Arg His Glu Ile Lys  
 115 120 125

Asp Thr Phe Leu Arg Thr Tyr Thr Asp Ala Met Gln Thr Tyr Asn Gly  
 130 135 140

Asn Asp Glu Arg Ser Arg Ala Val Asp His Val Gln Arg Xaa  
 145 150 155

421

<210> 471  
<211> 59  
<212> PRT  
<213> Homo sapiens

<400> 471  
Val Leu Phe Phe Tyr Glu Cys Pro Asn Leu Cys Phe Pro Leu Pro Ser  
1 5 10 15  
Gln Thr Val Trp Pro Val Glu Ser Val Trp Phe Val Phe Ile Ser Pro  
20 25 30  
Ser Phe Leu Glu Gln Gly Leu Arg Pro Cys His Ile Ser Tyr Ala Leu  
35 40 45  
His Pro Arg Leu Phe Trp Thr Leu Lys Val Asp  
50 55

<210> 472  
<211> 320  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (48)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (49)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (53)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (105)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 472  
Asp Pro Asp Glu Val Phe Pro Val Cys Leu Pro Leu Thr Gly Asp Ala  
1 5 10 15

Gly Glu Asp Gly Gly Lys Met Leu His Leu Pro Glu Trp Pro Glu Gln  
20 25 30

Pro Pro Gly Gly Pro Ala Ala Leu Gln Val Arg Gly Ala Glu Asp Xaa  
35 40 45

Xaa Leu Ser Phe Xaa Asp Cys Glu Ser Leu Gln Ala Val Phe Asp Pro  
50 55 60

Ala Ser Cys Pro His Met Leu Arg Ala Pro Ala Arg Val Leu Gly Glu  
65 70 75 80

Ala Val Leu Pro Phe Ser Pro Ala Leu Ala Glu Val Thr Leu Gly Ile  
85 90 95

Gly Arg Gly Ala Gly Ser Ser Trp Xaa Tyr His Glu Glu Glu Ala Asp  
100 105 110

Ser Thr Ala Lys Ala Met Val Thr Glu Met Cys Leu Gly Glu Glu Asp  
115 120 125

Phe Gln Gln Leu Gln Ala Gln Glu Gly Val Ala Ile Thr Phe Cys Leu  
130 135 140

Lys Glu Phe Arg Gly Leu Leu Ser Phe Ala Glu Ser Ala Asn Leu Asn  
145 150 155 160

Leu Ser Ile His Phe Asp Ala Pro Gly Arg Pro Ala Ile Phe Thr Ile  
165 170 175

Lys Asp Ser Leu Leu Asp Gly His Phe Val Leu Ala Thr Leu Ser Asp  
180 185 190

Thr Asp Ser His Ser Gln Asp Leu Gly Ser Pro Glu Arg His Gln Pro  
195 200 205

Val Pro Gln Leu Gln Ala His Ser Thr Pro His Pro Asp Asp Phe Ala  
210 215 220

Asn Asp Asp Ile Asp Ser Tyr Met Ile Ala Met Glu Thr Thr Ile Gly  
225 230 235 240

Asn Glu Gly Ser Arg Val Leu Pro Ser Ile Ser Leu Ser Pro Gly Pro  
245 250 255

Gln Pro Pro Lys Ser Pro Gly Pro His Ser Glu Glu Glu Asp Glu Ala  
260 265 270

Glu Pro Ser Thr Val Pro Gly Thr Pro Pro Pro Lys Lys Phe Arg Ser  
275 280 285

423

Leu Phe Phe Gly Ser Ile Leu Ala Pro Val Arg Ser Pro Gln Gly Pro  
 290 295 300

Ser Leu Cys Trp Arg Lys Thr Val Arg Val Lys Ala Glu Pro Arg Thr  
 305 310 315 320

<210> 473  
 <211> 331  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (24)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (283)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (299)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (324)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 473  
 Pro Pro Cys Ala Val Pro Gly Pro Arg Leu Ser Pro Lys Leu Arg Thr  
 1 5 10 15

Pro Ser Asn Ser Arg Glu Ser Xaa Ile Cys Val Ser Gly Arg Ala Glu  
 20 25 30

Ala Leu Thr Phe Arg His Gly Ala Glu Gly Ser Asp Arg Arg Arg Gln  
 35 40 45

Arg Arg Glu Gly Val Leu Gly Pro Ala Leu Leu Cys Arg Pro Trp Glu  
 50 55 60

Val Leu Gly Ala His Glu Val Pro Ser Arg Asn Ile Phe Ser Glu Gln

424

65		70		75		80
Thr Ile Pro Pro Ser Ala Lys Tyr Gly Gly Arg His Thr Val Thr Met						
	85		90		95	
Ile Pro Gly Asp Gly Ile Gly Pro Glu Leu Met Leu His Val Lys Ser						
	100		105		110	
Val Phe Arg His Ala Cys Val Pro Val Asp Phe Glu Glu Val His Val						
	115		120		125	
Ser Ser Asn Ala Asp Glu Glu Asp Ile Arg Asn Ala Ile Met Ala Ile						
	130		135		140	
Arg Arg Asn Arg Val Ala Leu Lys Gly Asn Ile Glu Thr Asn His Asn						
	145		150		155	160
Leu Pro Pro Ser His Lys Ser Arg Asn Asn Ile Leu Arg Thr Ser Leu						
	165		170		175	
Asp Leu Tyr Ala Asn Val Ile His Cys Lys Ser Leu Pro Gly Val Val						
	180		185		190	
Thr Arg His Lys Asp Ile Asp Ile Leu Ile Val Arg Glu Asn Thr Glu						
	195		200		205	
Gly Glu Tyr Ser Ser Leu Glu His Glu Ser Val Ala Gly Val Val Glu						
	210		215		220	
Ser Leu Lys Ile Ile Thr Lys Ala Lys Ser Leu Arg Ile Ala Glu Tyr						
	225		230		235	240
Ala Phe Lys Leu Ala Gln Glu Ser Gly Arg Lys Lys Val Thr Ala Val						
	245		250		255	
His Lys Ala Asn Ile Met Lys Leu Gly Asp Gly Leu Phe Leu Gln Cys						
	260		265		270	
Cys Arg Glu Val Ala Ala Arg Tyr Pro Gln Xaa Thr Phe Glu Asn Met						
	275		280		285	
Ile Val Asp Asn Thr Thr Met Gln Leu Val Xaa Arg Pro Gln Gln Phe						
	290		295		300	
Asp Val Met Val Met Pro Asn Leu Tyr Gly Asn Ile Val Lys Gln Cys						
	305		310		315	320
Leu Arg Gly Xaa Gly Arg Gly Pro Lys Leu Val						
	325		330			

425

&lt;210&gt; 474

&lt;211&gt; 30

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 474

Thr Pro Ile Ser Thr Lys Asn Thr Lys Ile Ser Gln Ala Arg Trp Arg  
1 5 10 15

Ala His Val Val Pro Ala Thr Arg Glu Ala Asp Ala Glu Glu  
20 25 30

&lt;210&gt; 475

&lt;211&gt; 124

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (110)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 475

Thr Gln Phe Ser Leu Ser Pro Val Glu Thr Ile Tyr Thr Ile Leu Cys  
1 5 10 15

Ile Asn Val Tyr Thr Leu Pro Ile Cys Ile His Ile Tyr Ile Val Tyr  
20 25 30

Ile Leu Tyr Met Tyr Arg Cys Val Tyr Val His Ile Tyr Thr His Ala  
35 40 45

His Asn Lys Ile Arg Cys Ser Leu Gln Ile Gln Met Leu Ile Thr Lys  
50 55 60

Pro Asp Ala Thr Gln Thr Ala Ala Glu Glu Thr Arg Leu Asp Ser Cys  
65 70 75 80

Asn Arg Ser Gln Lys Ile Lys Thr Ala Thr Cys Ser Asp Phe Gly His  
85 90 95

Phe Cys Met Phe Ile Lys Asn Gly Phe Val Thr Arg Lys Xaa Arg Thr  
100 105 110

Ser Val Ser Glu Lys Gly Arg Trp Gly Glu Pro Ser  
115 120

&lt;210&gt; 476

&lt;211&gt; 64

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 476

Asn Gly Tyr Leu Val Phe Pro Arg Lys Asn Ser Phe Leu Leu Ile Phe  
1 5 10 15

Gly Leu Phe Val Tyr Leu Glu Thr Asn Leu Asp Ser Leu Pro Leu Val  
20 25 30

Asp Thr His Ser Lys Arg Thr Leu Ile Lys Thr Val Glu Thr Arg  
35 40 45

Asp Gly Gln Val Ile Asn Glu Thr Ser Gln His His Asp Asp Leu Glu  
50 55 60

&lt;210&gt; 477

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 477

Val Leu Thr Val Asp Ala Arg Asn His Gly Asp Ser Pro His Ser Pro  
1 5 10 15

Asp Met Ser Tyr Glu Ile Met Ser Gln Asp Leu Gln Asp Leu Leu Pro  
20 25 30

Gln Leu Gly Leu Val Pro Cys Val Val Val Gly His Ser Met Gly Gly  
35 40 45

Lys Thr Ala Met Leu Leu Ala Leu Gln Arg Pro Glu Leu Val Glu Arg  
50 55 60

Leu Ile Ala Val Asp Ile Ser Pro Val Glu Ser Thr Gly Val Ser His  
65 70 75 80

Phe Ala Thr Tyr Val Ala Ala Met Arg Ala Ile Asn Ile Ala Asp Arg  
85 90 95

Leu Ala Pro Leu Pro Cys Pro Lys Thr Gly Gly  
100 105



427

&lt;210&gt; 478

&lt;211&gt; 282

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (281)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 478

Arg Glu Leu Gly Gly Thr Leu Leu Ser Ala Ile Glu Val Glu Gly Ala  
 1 5 10 15

Lys Met Gln Ser Asn Lys Thr Phe Asn Leu Glu Lys Gln Asn His Thr  
 20 25 30

Pro Arg Lys His His Gln His His His Gln Gln Gln His His Gln Gln  
 35 40 45

Gln Gln Gln Gln Pro Pro Pro Pro Ile Pro Ala Asn Gly Gln Gln  
 50 55 60

Ala Ser Ser Gln Asn Glu Gly Leu Thr Ile Asp Leu Lys Asn Phe Arg  
 65 70 75 80

Lys Pro Gly Glu Lys Thr Phe Thr Gln Arg Ser Arg Leu Phe Val Gly  
 85 90 95

Asn Leu Pro Pro Asp Ile Thr Glu Glu Glu Met Arg Lys Leu Phe Glu  
 100 105 110

Lys Tyr Gly Lys Ala Gly Glu Val Phe Ile His Lys Asp Lys Gly Phe  
 115 120 125

Gly Phe Ile Arg Leu Glu Thr Arg Thr Leu Ala Glu Ile Ala Lys Val  
 130 135 140

Glu Leu Asp Asn Met Pro Leu Arg Gly Lys Gln Leu Arg Val Arg Phe  
 145 150 155 160

Ala Cys His Ser Ala Ser Leu Thr Val Arg Asn Leu Pro Gln Tyr Val  
 165 170 175

Ser Asn Glu Leu Leu Glu Glu Ala Phe Ser Val Phe Gly Gln Val Glu  
 180 185 190

Arg Ala Val Val Ile Val Asp Asp Arg Gly Arg Pro Ser Gly Lys Gly  
 195 200 205

428

Ile Val Glu Phe Ser Gly Lys Pro Ala Ala Arg Lys Ala Leu Asp Arg  
 210 215 220

Cys Ser Glu Gly Ser Phe Leu Leu Thr Thr Phe Pro Arg Pro Val Thr  
 225 230 235 240

Val Glu Pro Met Asp Gln Leu Asp Asp Glu Glu Gly Leu Pro Glu Lys  
 245 250 255

Leu Val Ile Lys Asn Gln Gln Phe His Lys Glu Arg Glu Gln Pro Pro  
 260 265 270

Arg Phe Ala Gln Pro Gly Ser Phe Xaa Val  
 275 280

<210> 479  
 <211> 289  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (206)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (215)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (218)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (285)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 479  
 Ala Val Pro Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Val Cys  
 1 5 10 15

Gly Pro Leu Ser Ala Pro Arg Gly Ser Arg Arg Pro Thr Val Pro Gly  
 20 25 30

Thr Pro Ala Cys Leu Ala Arg Pro Ala Ala Gln Gly Phe Ser Ala Ala

429

35	40	45
Leu Pro Val Arg Trp Thr Gly Arg Arg Ala Gly Pro Ser Arg Pro Val		
50	55	60
Pro Ile Gly Thr Pro Ser Arg Ala Ala Asp Pro Ser Gln Gly Glu Met		
65	70	75 80
Ser Ala Asp Ala Ala Ala Gly Ala Pro Leu Pro Arg Leu Cys Cys Leu		
	85	90 95
Glu Lys Gly Pro Asn Gly Tyr Gly Phe His Leu His Gly Glu Lys Gly		
	100	105 110
Lys Leu Gly Gln Tyr Ile Arg Leu Val Glu Pro Gly Ser Pro Ala Glu		
	115	120 125
Lys Ala Gly Leu Leu Ala Gly Asp Arg Leu Val Glu Val Asn Gly Glu		
	130	135 140
Asn Val Glu Lys Glu Thr His Gln Gln Val Val Ser Arg Ile Arg Ala		
	145	150 155 160
Ala Leu Asn Ala Val Arg Leu Leu Val Val Asp Pro Glu Thr Asp Glu		
	165	170 175
Gln Leu Gln Lys Leu Gly Val Gln Val Arg Glu Glu Leu Leu Arg Ala		
	180	185 190
Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro Ala Ala Ala Xaa Val Gln		
	195	200 205
Gly Ala Gly Asn Glu Asn Xaa Pro Arg Xaa Ala Asp Lys Ser His Pro		
	210	215 220
Glu Gln Arg Glu Leu Arg Pro Arg Leu Cys Thr Met Lys Lys Gly Pro		
	225	230 235 240
Ser Gly Tyr Gly Phe Asn Leu His Ser Asp Lys Ser Lys Pro Gly Gln		
	245	250 255
Phe Ile Arg Ser Val Asp Pro Asp Ser Pro Ala Glu Ala Ser Gly Leu		
	260	265 270
Arg Ala Gln Asp Arg Ile Val Glu Val Met Leu Leu Xaa Ser Leu Pro		
	275	280 285
Ile		

430

&lt;210&gt; 480

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 480

Gly Ser Thr His Ala Ser Gly Arg Asn Glu Gly Pro Pro Ala Lys Thr  
1 5 10 15

Lys Ser Trp Val Gly Pro Thr Leu His Phe His Arg Lys Ser Glu His  
20 25 30

Leu Val Gly Leu Lys Val Leu Cys Cys Phe Arg Leu  
35 40

&lt;210&gt; 481

&lt;211&gt; 124

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (8)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 481

Ser Ile Xaa His Xaa Arg Lys Xaa Xaa Xaa Thr Val Arg Ser Asp Ser  
1 5 10 15

431

Arg Val Asp Pro Arg Ser Asp Asp Phe Thr Pro Leu Glu Ile Leu Trp  
20 25 30  
Thr Phe Ser Ile Tyr Leu Glu Ser Val Ala Ile Leu Pro Gln Leu Phe  
35 40 45  
Met Val Ser Lys Thr Gly Glu Ala Glu Thr Ile Thr Ser His Tyr Leu  
50 55 60  
Phe Ala Leu Gly Val Tyr Arg Thr Leu Tyr Leu Phe Asn Trp Ile Trp  
65 70 75 80  
Arg Tyr His Phe Glu Gly Phe Phe Asp Leu Ile Ala Ile Val Ala Gly  
85 90 95  
Leu Val Gln Thr Val Leu Tyr Cys Asp Phe Phe Tyr Leu Tyr Ile Thr  
100 105 110  
Lys Val Leu Lys Gly Lys Lys Leu Ser Leu Pro Ala  
115 120

&lt;210&gt; 482

&lt;211&gt; 131

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (122)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (127)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (131)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 482

Cys Ser Ser Arg Gly Ala His His Ser His Cys Asp Arg Leu Pro His

432

1                    5                    10                    15  
 Ser Pro Trp Pro Gly Leu Arg Glu Val Glu Leu Leu Ala Ser Val His  
                   20                    25                    30  
 Thr Glu Gln Met Glu Glu Glu Leu Ala Leu Gly Pro Arg Gly Gln Gly  
                   35                    40                    45  
 Gly Ala Ser Leu Ala Gly Arg Asp Gly Arg Ser Ala Gly Ala Gly Ser  
                   50                    55                    60  
 Tyr Gly Ala Leu Ala Asn Ser Ala Trp Gly Gly Pro Arg Lys Val Ala  
                   65                    70                    75                    80  
 Ser Ala Ser Ala Ala Ala Ser Thr Leu Ser Glu Pro Pro Arg Arg Thr  
                   85                    90                    95  
 Gln Glu Ser Arg Thr Arg Thr Arg Ala Leu Gly Leu Pro Thr Leu Pro  
                   100                    105                    110  
 Met Glu Lys Leu Ala Ala Ser Asn Arg Xaa Pro Xaa Gly Leu Xaa Gly  
                   115                    120                    125  
 Pro Gly Xaa  
                   130

<210> 483  
 <211> 221  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (168)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (174)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 483  
 Lys Lys Pro Pro Ile Thr His Pro Ser Thr Pro Ala Glu Glu Thr Tyr .  
   1                    5                    10                    15  
 Asn Leu Gly Arg Gln Val Leu Pro Leu Ser Ala Val Thr Tyr Phe Gln  
                   20                    25                    30  
 Lys Ser Gly Pro Gly Leu Leu Pro Ala Pro Ala Thr Gln Ser Ala Ser

433

35	40	45
Val Ala Gly Thr Leu Gln Asn Ser Leu Cys Ser Gln Val Thr Lys Lys		
50	55	60
Lys Arg Ala Asn Met Leu Val Leu Leu Ala Gly Ile Phe Val Val His		
65	70	75
Ile Ala Thr Val Ile Met Leu Phe Val Ser Thr Ile Ala Asn Val Trp		
85	90	95
Leu Val Ser Asn Thr Val Asp Ala Ser Val Gly Leu Trp Lys Asn Cys		
100	105	110
Thr Asn Ile Ser Cys Ser Asp Ser Leu Ser Tyr Ala Ser Glu Asp Ala		
115	120	125
Leu Lys Thr Val Gln Ala Phe Met Ile Leu Ser Ile Ile Phe Cys Val		
130	135	140
Ile Ala Leu Leu Val Phe Val Phe Gln Leu Phe Thr Met Glu Lys Gly		
145	150	155
Asn Arg Phe Phe Leu Ser Gly Xaa Thr Thr Leu Val Cys Xaa Leu Cys		
165	170	175
Ile Leu Val Gly Cys Pro Ser Thr Leu Val Ile Met Arg Ile Val Met		
180	185	190
Glu Arg Ile Cys Thr Thr Ala Ile Pro Thr Ser Trp Ala Gly Ser Ala		
195	200	205
Ser Ala Ser Ala Ser Ser Ser Ala Phe Ser Ile Trp Ser		
210	215	220

&lt;210&gt; 484

&lt;211&gt; 382

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (22)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (54)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (69)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (287)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (298)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (324)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (358)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 484  
 Thr Lys Leu Trp Thr Leu Val Ser Asn Pro Asp Thr Asp Ala Leu Ile  
   1                  5                  10                  15  
 Cys Trp Ser Pro Ser Xaa Asn Ser Phe His Val Phe Asp Gln Gly Gln  
                   20                  25                  30  
 Phe Ala Lys Glu Val Leu Pro Lys Tyr Phe Lys His Asn Asn Met Ala  
           35                  40                  45  
 Ser Phe Val Arg Gln Xaa Asn Met Tyr Gly Phe Arg Lys Val Val His  
   50                  55                  60  
 Ile Glu Gln Gly Xaa Leu Val Lys Pro Glu Arg Asp Asp Thr Glu Phe  
   65                  70                  75                  80  
 Gln His Pro Cys Phe Leu Arg Gly Gln Glu Gln Leu Leu Glu Asn Ile  
                   85                  90                  95  
 Lys Arg Lys Val Thr Ser Val Ser Thr Leu Lys Ser Glu Asp Ile Lys  
   100                  105                  110  
 Ile Arg Gln Asp Ser Val Thr Lys Leu Leu Thr Asp Val Gln Leu Met  
   115                  120                  125



435

Lys Gly Lys Gln Glu Cys Met Asp Ser Lys Leu Leu Ala Met Lys His  
 130 135 140  
 Glu Asn Glu Ala Leu Trp Arg Glu Val Ala Ser Leu Arg Gln Lys His  
 145 150 155 160  
 Ala Gln Gln Gln Lys Val Val Asn Lys Leu Ile Gln Phe Leu Ile Ser  
 165 170 175  
 Leu Val Gln Ser Asn Arg Ile Leu Gly Val Lys Arg Lys Ile Pro Leu  
 180 185 190  
 Met Leu Asn Asp Ser Gly Ser Ala His Ser Met Pro Lys Tyr Ser Arg  
 195 200 205  
 Gln Phe Ser Leu Glu His Val His Gly Ser Gly Pro Tyr Ser Ala Pro  
 210 215 220  
 Ser Pro Ala Tyr Ser Ser Ser Ser Leu Tyr Ala Pro Asp Ala Val Ala  
 225 230 235 240  
 Ser Ser Gly Pro Ile Ile Ser Asp Ile Thr Glu Leu Ala Pro Ala Ser  
 245 250 255  
 Pro Met Ala Ser Pro Gly Gly Ser Ile Asp Glu Arg Pro Leu Ser Ser  
 260 265 270  
 Ser Pro Leu Val Arg Val Lys Glu Glu Pro Pro Ser Pro Pro Xaa Ser  
 275 280 285  
 Pro Arg Val Glu Glu Ala Ser Pro Gly Xaa Pro Ser Ser Val Asp Thr  
 290 295 300  
 Leu Leu Ser Pro Thr Ala Leu Ile Asp Ser Ile Leu Arg Glu Ser Glu  
 305 310 315 320  
 Pro Ala Pro Xaa Ser Val Thr Ala Leu Thr Asp Ala Arg Gly His Thr  
 325 330 335  
 Asp Thr Glu Gly Arg Pro Pro Ser Pro Pro Pro Thr Ser Thr Pro Glu  
 340 345 350  
 Lys Cys Leu Ser Val Xaa Ala Trp Thr Arg Met Ser Ser Val Thr Thr  
 355 360 365  
 Trp Met Leu Trp Thr Pro Thr Trp Ile Thr Cys Arg Pro Cys  
 370 375 380

&lt;210&gt; 485

436

&lt;211&gt; 416

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (399)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 485

Pro	Ser	Val	Ala	Asn	Val	Gly	Ser	His	Cys	Asp	Leu	Ser	Leu	Lys	Ile
1				5					10					15	

Pro	Glu	Ile	Ser	Ile	Gln	Asp	Met	Thr	Ala	Gln	Val	Thr	Ser	Pro	Ser
		20					25						30		

Gly	Lys	Thr	His	Glu	Ala	Glu	Ile	Val	Glu	Gly	Glu	Asn	His	Thr	Tyr
	35						40					45			

Cys	Ile	Arg	Phe	Val	Pro	Ala	Glu	Met	Gly	Thr	His	Thr	Val	Ser	Val
	50					55					60				

Lys	Tyr	Lys	Gly	Gln	His	Val	Pro	Gly	Ser	Pro	Phe	Gln	Phe	Thr	Val
65					70					75					80

Gly	Pro	Leu	Gly	Glu	Gly	Gly	Ala	His	Lys	Val	Arg	Ala	Gly	Gly	Pro
				85					90					95	

Gly	Leu	Glu	Arg	Ala	Glu	Ala	Gly	Val	Pro	Ala	Glu	Phe	Ser	Ile	Trp
			100					105					110		

Thr	Arg	Glu	Ala	Gly	Ala	Gly	Gly	Leu	Ala	Ile	Ala	Val	Glu	Gly	Pro
		115					120					125			

Ser	Lys	Ala	Glu	Ile	Ser	Phe	Glu	Asp	Arg	Lys	Asp	Gly	Ser	Cys	Gly
	130					135					140				

Val	Ala	Tyr	Val	Val	Gln	Glu	Pro	Gly	Asp	Tyr	Glu	Val	Ser	Val	Lys
145					150				155						160

Phe	Asn	Glu	Glu	His	Ile	Pro	Asp	Ser	Pro	Phe	Val	Val	Pro	Val	Ala
				165					170					175	

Ser	Pro	Ser	Gly	Asp	Ala	Arg	Arg	Leu	Thr	Val	Ser	Ser	Leu	Gln	Glu
			180					185					190		

Ser	Gly	Leu	Lys	Val	Asn	Gln	Pro	Ala	Ser	Phe	Ala	Val	Ser	Leu	Asn
	195						200					205			

Gly	Ala	Lys	Gly	Ala	Ile	Asp	Ala	Lys	Val	His	Ser	Pro	Ser	Gly	Ala
	210					215						220			

437

Leu Glu Glu Cys Tyr Val Thr Glu Ile Asp Gln Asp Lys Tyr Ala Val  
 225 230 235 240  
 Arg Phe Ile Pro Arg Glu Asn Gly Val Tyr Leu Ile Asp Val Lys Phe  
 245 250 255  
 Asn Gly Thr His Ile Pro Gly Ser Pro Phe Lys Ile Arg Val Gly Glu  
 260 265 270  
 Pro Gly His Gly Gly Asp Pro Gly Leu Val Ser Ala Tyr Gly Ala Gly  
 275 280 285  
 Leu Glu Gly Gly Val Thr Gly Asn Pro Ala Glu Phe Val Val Asn Thr  
 290 295 300  
 Ser Asn Ala Gly Ala Gly Ala Leu Ser Val Thr Ile Asp Gly Pro Ser  
 305 310 315 320  
 Lys Val Lys Met Asp Cys Gln Glu Cys Pro Glu Gly Tyr Arg Val Thr  
 325 330 335  
 Tyr Thr Pro Met Ala Pro Gly Ser Tyr Leu Ile Ser Ile Lys Tyr Gly  
 340 345 350  
 Gly Pro Tyr His Ile Gly Gly Ser Pro Phe Lys Ala Lys Val Thr Gly  
 355 360 365  
 Pro Arg Leu Val Ser Asn His Ser Leu His Glu Thr Ser Ser Val Phe  
 370 375 380  
 Val Asp Ser Leu Thr Lys Ala Thr Cys Ala Pro Gln His Gly Xaa Pro  
 385 390 395 400  
 Gly Pro Gly Pro Ala Asp Ala Ser Lys Val Val Ala Lys Gly Trp Gly  
 405 410 415

&lt;210&gt; 486

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 486

Phe Val Thr Ser Gly Lys Ile Ser Leu Tyr Val Tyr Ile Leu Thr Ile  
 1 5 10 15

438

Arg Leu Asp Thr Asn Lys Ala Thr Leu Leu Thr Ala Ser Gly Glu Leu  
20 25 30

Ile Leu Phe Leu Ile Phe Phe Asn Lys Asp Ile Leu Arg Tyr  
35 40 45

&lt;210&gt; 487

&lt;211&gt; 162

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 487

Leu Gly Val Ala Leu Gly Ala Val Pro Lys Leu His Leu Gly Val Leu  
1 5 10 15

Val Ser Thr Gly Leu Arg Thr Ala Val Gly Ser Pro Arg Leu Pro Pro  
20 25 30

Thr Ala Leu Gly Ala Ala Tyr Gly Thr Ala Lys Ser Gly Thr Gly Ile  
35 40 45

Ala Ala Met Ser Val Met Arg Pro Glu Gln Ile Met Lys Ser Ile Ile  
50 55 60

Pro Val Val Met Ala Gly Ile Ile Ala Ile Tyr Gly Leu Val Val Ala  
65 70 75 80

Val Leu Ile Ala Asn Ser Leu Asn Asp Asp Ile Ser Leu Tyr Lys Ser  
85 90 95

Phe Leu Gln Leu Gly Ala Gly Leu Ser Val Gly Leu Ser Gly Leu Ala  
100 105 110

Ala Gly Phe Ala Ile Gly Ile Val Gly Asp Ala Gly Val Arg Gly Thr  
115 120 125

Ala Gln Gln Pro Arg Leu Phe Val Gly Met Ile Leu Ile Leu Ile Phe  
130 135 140

Ala Glu Val Leu Gly Leu Tyr Gly Leu Ile Val Ala Leu Ile Leu Ser  
145 150 155 160

Thr Lys

&lt;210&gt; 488

&lt;211&gt; 114

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (95)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (111)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (113)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 488

Gln Ala Leu Arg Pro Gly Ser Phe Arg Gly Thr Gly Arg Lys Arg Glu  
 1 5 10 15

Arg Glu Arg Glu Arg Met Ser Leu Ser Asp Trp His Leu Ala Val Lys  
 20 25 30

Leu Ala Asp Gln Pro Leu Ala Pro Lys Ser Ile Leu Gln Leu Pro Glu  
 35 40 45

Ser Glu Leu Gly Glu Tyr Ser Leu Gly Gly Tyr Ser Ile Ser Phe Leu  
 50 55 60

Lys Gln Leu Ile Ala Gly Lys Leu Gln Glu Ser Val Pro Asp Pro Glu  
 65 70 75 80

Leu Ile Asp Leu Ile Tyr Cys Gly Arg Lys Leu Lys Asp Asp Xaa Thr  
 85 90 95

Leu Thr Ser Thr Val Phe Asn Leu Ala Pro His Pro Cys Ser Xaa Glu  
 100 105 110

Xaa Leu

&lt;210&gt; 489

&lt;211&gt; 149

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

440

<221> SITE  
 <222> (121)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (142)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 489  
 Ser Thr His Ala Ser Glu Asp Val Leu Ala Ala Pro Ser Gly Cys Arg  
   1                  5                  10                  15  
  
 Ala Ser Arg Pro Pro Thr Ser Gly Arg Glu Gln Phe Trp Ala Arg Gly  
                   20                  25                  30  
  
 Leu Ala Ala Ala Asp Met Thr Lys Gly Leu Val Leu Gly Ile Tyr Ser  
           35                  40                  45  
  
 Lys Asp Lys Glu Asp Asp Val Pro Gln Phe Thr Ser Ala Gly Glu Asn  
       50                  55                  60  
  
 Phe Asp Lys Leu Val Ser Gly Lys Leu Arg Glu Ile Leu Asn Ile Ser  
   65                  70                  75                  80  
  
 Gly Pro Pro Leu Lys Ala Gly Lys Thr Arg Thr Phe Tyr Gly Leu His  
                   85                  90                  95  
  
 Glu Asp Phe Pro Ser Val Val Val Val Gly Leu Gly Arg Lys Ala Ala  
           100                  105                  110  
  
 Gly Val Asp Asp Gln Glu Asn Trp Xaa Glu Gly Lys Glu Asn Ile Arg  
       115                  120                  125  
  
 Val Ala Met Gln Arg Gly Ala Gly Arg Phe Gln Asp Leu Xaa Ile Ser  
       130                  135                  140  
  
 Ser Val Glu Gly Gly  
 145

<210> 490  
 <211> 527  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (311)  
 <223> Xaa equals any of the naturally occurring L-amino acids

441

&lt;400&gt; 490

Arg Arg Arg Ser Arg Gly Leu Ile Pro Gly Arg Ala Pro Gly Arg Arg  
 1 5 10 15

Arg Pro Arg Ala His Glu Val Ala Arg Ala Pro Pro Pro Ile Ala Met  
 20 25 30

Asp Arg Met Lys Lys Ile Lys Arg Gln Leu Ser Met Thr Leu Arg Gly  
 35 40 45

Gly Arg Gly Ile Asp Lys Thr Asn Gly Ala Pro Glu Gln Ile Gly Leu  
 50 55 60

Asp Glu Ser Gly Gly Gly Gly Gly Ser Asp Pro Gly Glu Ala Pro Thr  
 65 70 75 80

Arg Ala Ala Pro Gly Glu Leu Arg Ser Ala Arg Gly Pro Leu Ser Ser  
 85 90 95

Ala Pro Glu Ile Val His Glu Asp Leu Lys Met Gly Ser Asp Gly Glu  
 100 105 110

Ser Asp Gln Ala Ser Ala Thr Ser Ser Asp Glu Val Gln Ser Pro Val  
 115 120 125

Arg Val Arg Met Arg Asn His Pro Pro Arg Lys Ile Ser Thr Glu Asp  
 130 135 140

Ile Asn Lys Arg Leu Ser Leu Pro Ala Asp Ile Arg Leu Pro Glu Gly  
 145 150 155 160

Tyr Leu Glu Lys Leu Thr Leu Asn Ser Pro Ile Phe Asp Lys Pro Leu  
 165 170 175

Ser Arg Arg Leu Arg Arg Val Ser Leu Ser Glu Ile Gly Phe Gly Lys  
 180 185 190

Leu Glu Thr Tyr Ile Lys Leu Asp Lys Leu Gly Glu Gly Thr Tyr Ala  
 195 200 205

Thr Val Tyr Lys Gly Lys Ser Lys Leu Thr Asp Asn Leu Val Ala Leu  
 210 215 220

Lys Glu Ile Arg Leu Glu His Glu Glu Gly Ala Pro Cys Thr Ala Ile  
 225 230 235 240

Arg Glu Val Ser Leu Leu Lys Asp Leu Lys His Ala Asn Ile Val Thr  
 245 250 255

Leu His Asp Ile Ile His Thr Glu Lys Ser Leu Thr Leu Val Phe Glu

442

260					265					270						
Tyr	Leu	Asp	Lys	Asp	Leu	Lys	Gln	Tyr	Leu	Asp	Asp	Cys	Gly	Asn	Ile	
275					280					285						
Ile	Asn	Met	His	Asn	Val	Lys	Leu	Phe	Leu	Phe	Gln	Leu	Leu	Arg	Gly	
290					295					300						
Leu	Ala	Tyr	Cys	His	Arg	Xaa	Lys	Val	Leu	His	Arg	Asp	Leu	Lys	Pro	
305					310					315					320	
Gln	Asn	Leu	Leu	Ile	Asn	Glu	Arg	Gly	Glu	Leu	Lys	Leu	Ala	Asp	Phe	
325					330					335						
Gly	Leu	Ala	Arg	Ala	Lys	Ser	Ile	Pro	Thr	Lys	Thr	Tyr	Ser	Asn	Glu	
340					345					350						
Val	Val	Thr	Leu	Trp	Tyr	Arg	Pro	Pro	Asp	Ile	Leu	Leu	Gly	Ser	Thr	
355					360					365						
Asp	Tyr	Ser	Thr	Gln	Ile	Asp	Met	Trp	Gly	Val	Gly	Cys	Ile	Phe	Tyr	
370					375					380						
Glu	Met	Ala	Thr	Gly	Arg	Pro	Leu	Phe	Pro	Gly	Ser	Thr	Val	Glu	Glu	
385					390					395					400	
Gln	Leu	His	Phe	Ile	Phe	Arg	Ile	Leu	Gly	Thr	Pro	Thr	Glu	Glu	Thr	
405					410					415						
Trp	Pro	Gly	Ile	Leu	Ser	Asn	Glu	Glu	Phe	Lys	Thr	Tyr	Asn	Tyr	Pro	
420					425					430						
Lys	Tyr	Arg	Ala	Glu	Ala	Leu	Leu	Ser	His	Ala	Pro	Arg	Leu	Asp	Ser	
435					440					445						
Asp	Gly	Ala	Asp	Leu	Leu	Thr	Lys	Leu	Leu	Gln	Phe	Glu	Gly	Arg	Asn	
450					455					460						
Arg	Ile	Ser	Ala	Glu	Asp	Ala	Met	Lys	His	Pro	Phe	Phe	Leu	Ser	Leu	
465					470					475					480	
Gly	Glu	Arg	Ile	His	Lys	Leu	Pro	Asp	Thr	Thr	Ser	Ile	Phe	Ala	Leu	
485					490					495						
Lys	Glu	Ile	Gln	Leu	Gln	Lys	Glu	Ala	Ser	Leu	Arg	Ser	Ser	Ser	Met	
500					505					510						
Pro	Asp	Ser	Gly	Arg	Pro	Ala	Phe	Arg	Val	Val	Asp	Thr	Glu	Phe		
515					520					525						



<210> 491  
<211> 125  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (125)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 491  
Cys Thr Arg Ala His Pro Lys Asn Leu Val Glu Lys Gly Ile Leu Thr  
1 5 10 15  
Thr Glu Lys Gln Asn Phe Leu Leu Phe Asp Met Thr Thr His Pro Val  
20 25 30  
Thr Asn Thr Thr Glu Lys Gln Arg Leu Val Lys Lys Leu Gln Asp Ser  
35 40 45  
Val Leu Glu Arg Trp Val Asn Asp Pro Gln Arg Met Asp Lys Arg Thr  
50 55 60  
Leu Ala Leu Leu Val Leu Ala His Ser Ser Asp Val Leu Glu Asn Val  
65 70 75 80  
Phe Ser Ser Leu Thr Asp Asp Lys Tyr Asp Val Ala Met Asn Arg Ala  
85 90 95  
Lys Asp Leu Val Glu Leu Asp Pro Glu Val Glu Gly Thr Lys Pro Ser  
100 105 110  
Ala Thr Glu Met Ile Trp Ala Val Leu Ala Ala Phe Xaa  
115 120 125

<210> 492  
<211> 53  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (3)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (51)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 492

Val	Ser	Xaa	Ser	Ile	Leu	Ala	Leu	Leu	Phe	Asn	Thr	Asp	Ala	Leu	Phe
1				5					10					15	

Ser	Arg	Val	Tyr	Glu	Ser	Leu	Ser	Asp	Asn	His	Gly	Leu	Gln	Glu	Gln
			20					25					30		

Thr	Val	Glu	Lys	Leu	Phe	Phe	Gln	Trp	Lys	Ser	Trp	Val	Gln	Glu	Met
		35					40					45			

Xaa	Gly	Xaa	Leu	Lys
				50

<210> 493

<211> 82

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (60)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (67)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

445

&lt;400&gt; 493

Pro Gly Phe Phe Phe Gln Met Leu Val His Thr Tyr Ser Ser Met Asp  
 1 5 10 15  
 Arg His Asp Gly Val Pro Ser His Ser Ser Arg Leu Ser Gln Leu Gly  
 20 25 30  
 Ser Val Ser Gln Gly Pro Tyr Ser Ser Ala Pro Pro Leu Ser His Thr  
 35 40 45  
 Pro Ser Ser Asp Phe Gln Pro Pro Tyr Phe Pro Xaa Pro Tyr Gln Pro  
 50 55 60  
 Leu Pro Xaa Xaa Gln Ser Gln Asp Pro Tyr Ser His Val Xaa Xaa Pro  
 65 70 75 80  
 Tyr Pro

&lt;210&gt; 494

&lt;211&gt; 290

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 494

Tyr Lys Asp Trp Leu Thr Lys Met Ser Gly Lys His Asp Val Gly Ala  
 1 5 10 15  
 Tyr Met Leu Met Tyr Lys Gly Ala Asn Arg Thr Glu Thr Val Thr Ser  
 20 25 30  
 Phe Arg Lys Arg Glu Ser Lys Val Pro Ala Asp Leu Leu Lys Arg Ala  
 35 40 45  
 Phe Val Arg Met Ser Thr Ser Pro Glu Ala Phe Leu Ala Leu Arg Ser  
 50 55 60  
 His Phe Ala Ser Ser His Ala Leu Ile Cys Ile Ser His Trp Ile Leu  
 65 70 75 80  
 Gly Ile Gly Asp Arg His Leu Asn Asn Phe Met Val Ala Met Glu Thr  
 85 90 95  
 Gly Gly Val Ile Gly Ile Asp Phe Gly His Ala Phe Gly Ser Ala Thr  
 100 105 110  
 Gln Phe Leu Pro Val Pro Glu Leu Met Pro Phe Arg Leu Thr Arg Gln  
 115 120 125

Phe Ile Asn Leu Met Leu Pro Met Lys Glu Thr Gly Leu Met Tyr Ser  
 130 135 140  
 Ile Met Val His Ala Leu Arg Ala Phe Arg Ser Asp Pro Gly Leu Leu  
 145 150 155 160  
 Thr Asn Thr Met Asp Val Phe Val Lys Glu Pro Ser Phe Asp Trp Lys  
 165 170 175  
 Asn Phe Glu Gln Lys Met Leu Lys Lys Gly Gly Ser Trp Ile Gln Glu  
 180 185 190  
 Ile Asn Val Ala Glu Lys Asn Trp Tyr Pro Arg Gln Lys Ile Cys Tyr  
 195 200 205  
 Ala Lys Arg Lys Leu Ala Gly Ala Asn Pro Ala Val Ile Thr Cys Asp  
 210 215 220  
 Glu Leu Leu Leu Gly His Glu Lys Ala Pro Ala Phe Arg Asp Tyr Val  
 225 230 235 240  
 Ala Val Ala Arg Gly Ser Lys Asp His Asn Ile Arg Ala Gln Glu Pro  
 245 250 255  
 Glu Ser Gly Leu Ser Glu Glu Thr Gln Val Lys Cys Leu Met Asp Gln  
 260 265 270  
 Ala Thr Asp Pro Asn Ile Leu Gly Arg Thr Trp Glu Gly Trp Glu Pro  
 275 280 285  
 Trp Met  
 290

&lt;210&gt; 495

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; {148}

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 495

Cys Gln Ser His Pro Leu Pro Gly Gly Pro Ala Cys Pro Cys Leu Ala  
 1 5 10 15

Cys His Ile Thr Leu Leu Phe Gly Arg Pro Trp Leu Ile Lys Glu Val

447

	20		25		30
Leu Val Val Ser Gln Ala Lys Trp Asn Leu Glu Thr Val Lys Lys Val					
35		40		45	
Gln Ile Thr Leu Asn Cys Ile Gln Glu Val His Phe Phe Pro Ile Val					
50		55		60	
Arg Gly Ser Trp Ser Leu Arg Asp Ala Arg Leu Glu Ser Asp Tyr Ile					
65		70		75	80
Ile Ile Gln Asn Gly Asn Ser Gln Gly Asn Ala Phe Phe His Phe Ile					
	85		90		95
Arg Phe Phe Tyr Pro His Cys Thr Pro Ser Pro Ser Pro Leu Pro Ile					
	100		105		110
Trp Met Ala Ser Gln Lys Leu Gly Pro Ser Pro Pro Cys Leu Gly Gly					
	115		120		125
Gly Gln Ser Pro Leu Thr Ala Glu Ala Ala Leu Leu Ser Ser Ala Val					
	130		135		140
Leu Pro Leu Xaa Lys Cys Leu Gln Arg Val Met Ser					
145		150		155	

&lt;210&gt; 496

&lt;211&gt; 251

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 496

Glu Glu Leu Leu Arg Ala Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro					
1		5		10	15
Ala Ala Ala Glu Val Gln Gly Ala Gly Asn Glu Asn Glu Pro Arg Glu					
	20		25		30
Ala Asp Lys Ser His Pro Glu Gln Arg Xaa Leu Arg Pro Arg Leu Cys					
	35		40		45
Thr Met Lys Lys Gly Pro Ser Gly Tyr Gly Phe Asn Leu His Ser Asp					
	50		55		60

Lys Ser Lys Pro Gly Gln Phe Ile Arg Ser Val Asp Pro Asp Ser Pro  
 65 70 75 80  
 Ala Glu Ala Ser Gly Leu Arg Ala Gln Asp Arg Ile Val Glu Val Asn  
 85 90 95  
 Gly Val Cys Met Glu Gly Lys Gln His Gly Asp Val Val Ser Ala Ile  
 100 105 110  
 Arg Ala Gly Gly Asp Glu Thr Lys Leu Leu Val Val Asp Arg Glu Thr  
 115 120 125  
 Asp Glu Phe Phe Lys Lys Cys Arg Val Ile Pro Ser Gln Glu His Leu  
 130 135 140  
 Asn Gly Pro Leu Pro Val Pro Phe Thr Asn Gly Glu Ile Gln Lys Glu  
 145 150 155 160  
 Asn Ser Arg Glu Ala Leu Ala Glu Ala Ala Leu Glu Ser Pro Arg Pro  
 165 170 175  
 Ala Leu Val Arg Ser Ala Ser Ser Asp Thr Ser Glu Glu Leu Asn Ser  
 180 185 190  
 Gln Asp Ser Pro Pro Lys Gln Asp Ser Thr Ala Pro Ser Ser Thr Ser  
 195 200 205  
 Ser Ser Asp Pro Ile Leu Asp Phe Asn Ile Ser Leu Ala Met Ala Lys  
 210 215 220  
 Glu Arg Ala His Gln Lys Arg Ser Ser Lys Arg Ala Pro Gln Met Asp  
 225 230 235 240  
 Trp Ser Lys Lys Asn Glu Leu Phe Ser Asn Leu  
 245 250

&lt;210&gt; 497

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 497

Asn Gly Ala Glu Ala Val Ser Thr Glu Ala Lys Met Thr Ala Phe Pro  
 1 5 10 15  
 Asp Trp Pro Trp Leu Phe His Thr Leu Cys Asp Pro Cys Pro Met Thr  
 20 25 30  
 Leu Trp Leu Thr Leu Pro Glu Ala Met Thr Thr Ala Ala Phe Cys His

35

40

45

&lt;210&gt; 498

&lt;211&gt; 373

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (337)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (372)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 498

Gly Thr Arg Gly Ser Arg Ala Ser Gly Val Cys Ala Arg Gly Cys Leu  
 1 5 10 15

Asp Ser Ala Gly Pro Trp Thr Met Ser Arg Ala Leu Arg Pro Pro Leu  
 20 25 30

Pro Pro Leu Cys Phe Phe Leu Leu Leu Ala Ala Ala Gly Ala Arg  
 35 40 45

Ala Gly Gly Tyr Glu Thr Cys Pro Thr Val Gln Pro Asn Met Leu Asn  
 50 55 60

Val His Leu Leu Pro His Thr His Asp Asp Val Gly Trp Leu Lys Thr  
 65 70 75 80

Val Asp Gln Tyr Phe Tyr Gly Ile Lys Asn Asp Ile Gln His Ala Gly  
 85 90 95

Val Gln Tyr Ile Leu Asp Ser Val Ile Ser Ala Leu Leu Ala Asp Pro  
 100 105 110

Thr Arg Arg Phe Ile Tyr Val Glu Ile Ala Phe Phe Ser Arg Trp Trp  
 115 120 125

His Gln Gln Thr Asn Ala Thr Gln Glu Val Val Arg Asp Leu Val Arg  
 130 135 140

Gln Gly Arg Leu Glu Phe Ala Asn Gly Gly Trp Val Met Asn Asp Glu

450

145	150	155	160
Ala Ala Thr His Tyr Gly Ala Ile Val Asp Gln Met Thr Leu Gly Leu	165	170	175
Arg Phe Leu Glu Asp Thr Phe Gly Asn Asp Gly Arg Pro Arg Val Ala	180	185	190
Trp His Ile Asp Pro Phe Gly His Ser Arg Glu Gln Ala Ser Leu Phe	195	200	205
Ala Gln Met Gly Phe Asp Gly Phe Phe Phe Gly Arg Leu Asp Tyr Gln	210	215	220
Asp Lys Trp Val Arg Met Gln Lys Leu Glu Met Glu Gln Val Trp Arg	225	230	235
Ala Ser Thr Ser Leu Lys Pro Pro Thr Ala Asp Leu Phe Thr Gly Val	245	250	255
Leu Pro Asn Gly Tyr Asn Pro Pro Arg Asn Leu Cys Trp Asp Val Leu	260	265	270
Cys Val Asp Gln Pro Leu Val Glu Asp Pro Arg Ser Pro Glu Tyr Asn	275	280	285
Ala Lys Glu Leu Val Asp Tyr Phe Leu Asn Val Ala Thr Ala Gln Gly	290	295	300
Arg Tyr Tyr Arg Thr Asn His Thr Val Met Thr Met Gly Ser Asp Phe	305	310	315
Gln Tyr Glu Asn Ala Asn Met Trp Phe Lys Asn Leu Asp Lys Leu Ile	325	330	335
Xaa Leu Val Asn Ala Gln Gly Lys Arg Lys Gln Cys Pro Cys Ser Leu	340	345	350
Leu His Pro Arg Leu Leu Pro Leu Gly Ala Glu Gln Gly Gln Pro His	355	360	365
Leu Val Ser Xaa Thr	370		

&lt;210&gt; 499

&lt;211&gt; 238

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens



451

&lt;400&gt; 499

Ala Leu Pro Gly Pro Asp Trp His Gly Ala Gly Ala Ala Asp Arg Gly  
1 5 10 15  
Pro Ala Ala Pro Pro Arg Pro Gly Pro Cys Ala Tyr Ala Ala His Gly  
20 25 30  
Arg Gly Ala Leu Ala Glu Ala Ala Arg Arg Cys Leu His Asp Ile Ala  
35 40 45  
Leu Ala His Arg Ala Ala Thr Ala Ala Arg Pro Pro Ala Pro Pro Pro  
50 55 60  
Ala Pro Gln Pro Pro Ser Pro Thr Pro Ser Pro Pro Arg Pro Thr Leu  
65 70 75 80  
Ala Arg Glu Asp Asn Glu Glu Asp Glu Asp Glu Pro Thr Glu Thr Glu  
85 90 95  
Thr Ser Gly Glu Gln Leu Gly Ile Ser Asp Asn Gly Gly Leu Phe Val  
100 105 110  
Met Asp Glu Asp Ala Thr Leu Gln Asp Leu Pro Pro Phe Cys Glu Ser  
115 120 125  
Asp Pro Glu Ser Thr Asp Asp Gly Ser Leu Ser Glu Glu Thr Pro Ala  
130 135 140  
Gly Pro Pro Thr Cys Ser Val Pro Pro Ala Ser Ala Leu Pro Thr Gln  
145 150 155 160  
Gln Tyr Ala Lys Ser Leu Pro Val Ser Val Pro Val Trp Gly Phe Lys  
165 170 175  
Glu Lys Arg Thr Glu Ala Arg Ser Ser Asp Glu Glu Asn Gly Pro Pro  
180 185 190  
Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala Ser Met Arg Ala Leu Val  
195 200 205  
Leu Arg Glu Ala Glu Asp Thr Gln Val Phe Gly Asp Leu Pro Arg Pro  
210 215 220  
Arg Leu Asn Thr Ser Asp Phe Gln Lys Leu Lys Arg Lys Tyr  
225 230 235

&lt;210&gt; 500

&lt;211&gt; 198

&lt;212&gt; PRT

<220>

<221> SITE

&lt;222&gt; (94)

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

<221> SITE

<222> (156)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 500

Asn Ser Ala Glu Leu Ser Pro Gly Leu Cys Ser Pro Thr Pro Thr Glu  
1 5 10 15

Ala Arg Ala Gly Asp Ala Gly Pro Ala Ala Arg Ser Arg Lys Gln Asn  
20 25 30

Pro Gln Ser Pro Pro Cys Cys Cys Val Asp Asp Thr Trp Ala Gln Ala  
35 40 45

Glu Val Gly Pro Val Thr Ser Cys Thr Gly Phe Val Glu Gly Ser Ser  
50 55 60

Arg Thr Gly Gly Met Gly Ser Ala Cys Ile Lys Val Thr Lys Tyr Phe  
65 70 75 80

Leu Phe Leu Phe Asn Leu Ile Phe Phe Ile Leu Gly Ala Xaa Ile Leu  
85 90 95

Gly Phe Gly Val Trp Ile Leu Ala Asp Lys Ser Ser Phe Ile Ser Val  
100 105 110

Leu Gln Thr Ser Ser Ser Ser Leu Arg Met Gly Ala Tyr Val Phe Ile  
115 120 125

Gly Val Gly Ala Val Thr Met Leu Met Gly Phe Leu Gly Cys Ile Gly  
130 135 140

Ala Val Asn Glu Val Arg Cys Leu Leu Gly Leu Xaa Phe Ala Phe Leu  
145                      150                      155                      160

Leu Leu Ile Leu Ile Ala Gln Val Thr Ala Gly Ala Leu Phe Tyr Phe  
165 170 175

Asn Met Gly Lys Val Ser Pro Ser Leu Pro Pro Ser Ser Leu Gly Trp  
180 185 190

Thr Asn His Gly Gly Asp  
195

<210> 501  
<211> 169  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (165)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 501  
Ser Ser Ala Ser Thr Asn Met Ser Arg Gly Ser Ser Ala Gly Phe Asp  
1 5 10 15  
Arg His Ile Thr Ile Phe Ser Pro Glu Gly Arg Leu Tyr Gln Val Glu  
20 25 30  
Tyr Ala Phe Lys Ala Ile Asn Gln Gly Gly Leu Thr Ser Val Ala Val  
35 40 45  
Arg Gly Lys Asp Cys Ala Val Ile Val Thr Gln Lys Lys Val Pro Asp  
50 55 60  
Lys Leu Leu Asp Ser Ser Thr Val Thr His Leu Phe Lys Ile Thr Glu  
65 70 75 80  
Asn Ile Gly Cys Val Met Thr Gly Met Thr Ala Asp Ser Arg Ser Gln  
85 90 95  
Val Gln Arg Ala Arg Tyr Glu Ala Ala Asn Trp Lys Tyr Lys Tyr Gly  
100 105 110  
Tyr Glu Ile Pro Val Asp Met Leu Cys Lys Arg Ile Ala Asp Ile Ser  
115 120 125  
Gln Val Tyr Thr Gln Asn Ala Glu Met Arg Pro Leu Gly Cys Cys Met  
130 135 140  
Ile Leu Ile Gly Ile Asp Glu Glu Gln Gly Pro Gln Val Tyr Lys Cys  
145 150 155 160  
Asp Pro Ala Gly Xaa Tyr Cys Gly Val  
165

<210> 502  
<211> 507

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (361)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (461)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 502

Val	Arg	Gln	Leu	Cys	Arg	Pro	Ala	Glu	Xaa	Asp	Ser	Val	Met	Ala	Glu
1				5					10					15	

Gln	Val	Ala	Leu	Ser	Arg	Thr	Gln	Val	Cys	Gly	Ile	Leu	Arg	Glu	Glu
			20					25					30		

Leu	Phe	Gln	Gly	Asp	Ala	Phe	His	Gln	Ser	Asp	Thr	His	Ile	Phe	Ile
		35					40					45			

Ile	Met	Gly	Ala	Ser	Gly	Asp	Leu	Ala	Lys	Lys	Lys	Ile	Tyr	Pro	Thr
	50					55						60			

Ile	Trp	Trp	Leu	Phe	Arg	Asp	Gly	Leu	Leu	Pro	Glu	Asn	Thr	Phe	Ile
65					70					75				80	

Val	Gly	Tyr	Ala	Arg	Ser	Arg	Leu	Thr	Val	Ala	Asp	Ile	Arg	Lys	Gln
				85					90					95	

Ser	Glu	Pro	Phe	Phe	Lys	Ala	Thr	Pro	Glu	Glu	Lys	Leu	Lys	Leu	Glu
		100						105					110		

Asp	Phe	Phe	Ala	Arg	Asn	Ser	Tyr	Val	Ala	Gly	Gln	Tyr	Asp	Asp	Ala
	115						120					125			

Ala	Ser	Tyr	Gln	Arg	Leu	Asn	Ser	His	Met	Asn	Ala	Leu	His	Leu	Gly
	130					135					140				

Ser	Gln	Ala	Asn	Arg	Leu	Phe	Tyr	Leu	Ala	Leu	Pro	Pro	Thr	Val	Tyr
145					150					155				160	

Glu	Ala	Val	Thr	Lys	Asn	Ile	His	Glu	Ser	Cys	Met	Ser	Gln	Ile	Gly
				165					170					175	

Trp Asn Arg Ile Ile Val Glu Lys Pro Phe Gly Arg Asp Leu Gln Ser  
 180 185 190  
 Ser Asp Arg Leu Ser Asn His Ile Ser Ser Leu Phe Arg Glu Asp Gln  
 195 200 205  
 Ile Tyr Arg Ile Asp His Tyr Leu Gly Lys Glu Met Val Gln Asn Leu  
 210 215 220  
 Met Val Leu Arg Phe Ala Asn Arg Ile Phe Gly Pro Ile Trp Asn Arg  
 225 230 235 240  
 Asp Asn Ile Ala Cys Val Ile Leu Thr Phe Lys Glu Pro Phe Gly Thr  
 245 250 255  
 Glu Gly Arg Gly Gly Tyr Phe Asp Glu Phe Gly Ile Ile Arg Asp Val  
 260 265 270  
 Met Gln Asn His Leu Leu Gln Met Leu Cys Leu Val Ala Met Glu Lys  
 275 280 285  
 Pro Ala Ser Thr Asn Ser Asp Asp Val Arg Asp Glu Lys Val Lys Val  
 290 295 300  
 Leu Lys Cys Ile Ser Glu Val Gln Ala Asn Asn Val Val Leu Gly Gln  
 305 310 315 320  
 Tyr Val Gly Asn Pro Asp Gly Glu Gly Glu Ala Thr Lys Gly Tyr Leu  
 325 330 335  
 Asp Asp Pro Thr Val Pro Arg Gly Ser Thr Thr Ala Thr Phe Ala Ala  
 340 345 350  
 Val Val Leu Tyr Val Glu Asn Glu Xaa Trp Asp Gly Val Pro Phe Ile  
 355 360 365  
 Leu Arg Cys Gly Lys Ala Leu Asn Glu Arg Lys Ala Glu Val Arg Leu  
 370 375 380  
 Gln Phe His Asp Val Ala Gly Asp Ile Phe His Gln Gln Cys Lys Arg  
 385 390 395 400  
 Asn Glu Leu Val Ile Arg Val Gln Pro Asn Glu Ala Val Tyr Thr Lys  
 405 410 415  
 Met Met Thr Lys Lys Pro Gly Met Phe Phe Asn Pro Glu Glu Ser Glu  
 420 425 430  
 Leu Asp Leu Thr Tyr Gly Asn Arg Tyr Lys Asn Val Lys Leu Pro Asp  
 435 440 445

Ala Tyr Glu Arg Leu Ile Leu Asp Val Phe Cys Gly Xaa Gln Met His  
 450 455 460

Phe Val Arg Arg Thr Ser Ser Val Arg Pro Gly Val Phe Ser Pro His  
 465 470 475 480

Cys Cys Thr Arg Leu Ser Trp Arg Ser Pro Ser Pro Ser Pro Ile Phe  
 485 490 495

Met Ala Ala Glu Ala Pro Arg Arg Gln Thr Ser  
 500 505

<210> 503

<211> 260

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (69)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 503

Gly Pro Glu Val Leu Pro Glu Pro Arg Val Pro Arg Glu Ala Leu Ala  
 1 5 10 15

Phe Ile Ile Arg Ser Phe Gly Gly Glu Val Ser Trp Asp Lys Ser Leu  
 20 25 30

Cys Ile Gly Ala Thr Tyr Asp Val Thr Asp Ser Arg Ile Thr His Gln  
 35 40 45

Ile Val Asp Arg Pro Gly Gln Gln Thr Ser Val Ile Gly Arg Cys Tyr  
 50 55 60

Val Gln Pro Gln Xaa Val Phe Asp Ser Val Asn Ala Arg Leu Leu Leu  
 65 70 75 80

Pro Val Ala Glu Tyr Phe Ser Gly Val Gln Leu Pro Pro His Leu Ser  
 85 90 95

Pro Phe Val Thr Glu Lys Glu Gly Asp Tyr Val Pro Pro Glu Lys Leu  
 100 105 110

Lys Leu Leu Ala Leu Gln Arg Gly Glu Asp Pro Gly Asn Leu Asn Glu  
 115 120 125

Ser Glu Glu Glu Glu Glu Asp Asp Asn Asn Glu Gly Asp Gly Asp

130                      135                      140  
 Glu Glu Gly Glu Asn Glu Glu Glu Glu Asp Ala Glu Ala Gly Ser  
 145                      150                      155                      160  
 Glu Lys Glu Glu Glu Ala Arg Leu Ala Ala Leu Glu Glu Gln Arg Met  
                     165                      170                      175  
 Glu Gly Lys Lys Pro Arg Val Met Ala Gly Thr Leu Lys Leu Glu Asp  
                     180                      185                      190  
 Lys Gln Arg Leu Ala Gln Glu Glu Glu Ser Glu Ala Lys Arg Leu Ala  
                     195                      200                      205  
 Ile Met Met Met Lys Lys Arg Glu Lys Tyr Leu Tyr Gln Lys Ile Met  
                     210                      215                      220  
 Phe Gly Lys Arg Arg Lys Ile Arg Glu Ala Asn Lys Leu Ala Glu Lys  
 225                      230                      235                      240  
 Arg Lys Ala His Asp Glu Ala Val Arg Ser Glu Lys Lys Ala Lys Lys  
                     245                      250                      255  
 Ala Arg Pro Glu  
                     260

<210> 504  
 <211> 424  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (292)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (342)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 504  
 Leu Leu Gln Arg Cys Tyr Ala Phe Pro Gly His Arg Leu Ala His Ser  
   1                    5                    10                    15  
 Gly Ser Asp Leu Ser Leu Leu Val Pro Glu Ile Glu Asp Met Tyr Ser  
                     20                    25                    30  
 Ser Pro Tyr Leu Arg Pro Ser Glu Ser Pro Ile Thr Val Glu Val Asn

Cys	Thr	Asn	Pro	Gly	Thr	Arg	Tyr	Cys	Trp	Met	Ser	Thr	Gly	Leu	Tyr
50						55			60						
Ile	Pro	Gly	Arg	Gln	Ile	Ile	Glu	Val	Ser	Leu	Pro	Glu	Ala	Ala	Ala
65						70			75			80			
Ser	Ala	Asp	Leu	Lys	Ile	Gln	Ile	Gly	Cys	His	Thr	Asp	Asp	Leu	Thr
			85						90			95			
Arg	Ala	Ser	Lys	Leu	Phe	Arg	Gly	Pro	Leu	Val	Ile	Asn	Arg	Cys	Cys
			100						105			110			
Leu	Asp	Lys	Pro	Thr	Lys	Ser	Ile	Thr	Cys	Leu	Trp	Gly	Gly	Leu	Leu
115						120						125			
Tyr	Ile	Ile	Val	Pro	Gln	Asn	Ser	Lys	Leu	Gly	Ser	Val	Pro	Val	Thr
130						135						140			
Val	Lys	Gly	Ala	Val	His	Ala	Pro	Tyr	Tyr	Lys	Leu	Gly	Glu	Thr	Thr
145			150						155			160			
Leu	Glu	Glu	Trp	Lys	Arg	Arg	Ile	Gln	Glu	Asn	Pro	Gly	Pro	Trp	Gly
			165						170			175			
Glu	Leu	Ala	Thr	Asp	Asn	Ile	Ile	Leu	Thr	Val	Pro	Thr	Ala	Asn	Leu
			180						185			190			
Arg	Thr	Leu	Glu	Asn	Pro	Glu	Pro	Leu	Leu	Arg	Leu	Trp	Asp	Glu	Val
195						200						205			
Met	Gln	Ala	Val	Ala	Arg	Leu	Gly	Ala	Glu	Pro	Phe	Pro	Leu	Arg	Leu
210						215						220			
Pro	Gln	Arg	Ile	Val	Ala	Asp	Val	Gln	Ile	Ser	Val	Gly	Trp	Met	His
225			230						235			240			
Ala	Gly	Tyr	Pro	Ile	Met	Cys	His	Leu	Glu	Ser	Val	Gln	Glu	Leu	Ile
			245						250			255			
Asn	Glu	Lys	Leu	Ile	Arg	Thr	Lys	Gly	Leu	Trp	Gly	Pro	Val	His	Glu
260						265						270			
Leu	Gly	Arg	Asn	Gln	Gln	Arg	Gln	Glu	Trp	Glu	Phe	Pro	Pro	His	Thr
275						280						285			
Thr	Glu	Ala	Xaa	Cys	Asn	Leu	Trp	Cys	Val	Tyr	Val	His	Glu	Thr	Val
290						295						300			
Leu	Gly	Ile	Pro	Arg	Ser	Arg	Ala	Asn	Ile	Ala	Leu	Trp	Pro	Pro	Val



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<210> 505
<211> 70
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (49)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (54)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (66)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (70)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 505

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460

Leu His Gln Ser Leu Leu His Leu Glu Lys Thr Asn Glu Arg Lys Ser  
 1 5 10 15  
 Ile Phe Leu Ile His Tyr Pro Asn Asn Asn Arg Thr Pro Tyr Arg Asn  
 20 25 30  
 Tyr Tyr His Tyr Val Ser Lys His Tyr Ile Pro Ile Thr Tyr Pro Thr  
 35 40 45  
 Xaa Ser Ile Ile Asp Xaa Ile Ser Ile Pro Thr Met Ile Ser Ala Leu  
 50 55 60  
 Asn Xaa Gln Asn Lys Xaa  
 65 70

&lt;210&gt; 506

&lt;211&gt; 434

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (135)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (363)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 506

Ser Thr His Ala Ser Ala His Ala Ser Val Ser Thr Ala Ala Ala Ala  
 1 5 10 15  
 Ala Leu Ala Ala Ala Val Lys Ala Lys His Leu Ala Ala Val Glu  
 20 25 30  
 Glu Arg Lys Ile Lys Ser Leu Val Ala Leu Leu Val Glu Thr Gln Met  
 35 40 45  
 Lys Lys Leu Glu Ile Lys Leu Arg His Phe Glu Glu Leu Glu Thr Ile  
 50 55 60  
 Met Asp Arg Glu Xaa Glu Ala Leu Glu Tyr Gln Arg Gln Gln Leu Leu

65	70	75	80
Ala Asp Arg Gln Ala Phe His Met Glu Gln Leu Lys Tyr Ala Glu Met			
85	90	95	
Arg Ala Arg Gln Gln His Phe Gln Gln Met His Gln Gln Gln Gln			
100	105	110	
Pro Pro Pro Ala Leu Pro Pro Gly Ser Gln Pro Ile Pro Pro Thr Gly			
115	120	125	
Ala Ala Gly Pro Pro Ala Xaa His Gly Leu Ala Val Ala Pro Ala Ser			
130	135	140	
Val Val Pro Ala Pro Ala Gly Ser Gly Ala Pro Pro Gly Ser Leu Gly			
145	150	155	160
Pro Ser Glu Gln Ile Gly Gln Ala Gly Ser Thr Ala Gly Pro Gln Gln			
165	170	175	
Gln Gln Pro Ala Gly Ala Pro Gln Pro Gly Ala Val Pro Pro Gly Val			
180	185	190	
Pro Pro Pro Gly Pro His Gly Pro Ser Pro Phe Pro Asn Gln Gln Thr			
195	200	205	
Pro Pro Ser Met Met Pro Gly Ala Val Pro Gly Ser Gly His Pro Gly			
210	215	220	
Val Ala Gly Asn Ala Pro Leu Gly Leu Pro Phe Gly Met Pro Pro Pro			
225	230	235	240
Pro Pro Pro Pro Ala Pro Ser Ile Ile Pro Phe Gly Ser Leu Ala Asp			
245	250	255	
Ser Ile Ser Ile Asn Leu Pro Ala Pro Pro Asn Leu His Gly His His			
260	265	270	
His His Leu Pro Phe Ala Pro Gly Thr Leu Pro Pro Pro Asn Leu Pro			
275	280	285	
Val Ser Met Ala Asn Pro Leu His Pro Asn Leu Pro Ala Thr Thr Thr			
290	295	300	
Met Pro Ser Ser Leu Pro Leu Gly Pro Gly Leu Gly Ser Ala Ala Ala			
305	310	315	320
Gln Ser Pro Ala Ile Val Ala Ala Val Gln Gly Asn Leu Leu Pro Ser			
325	330	335	
Ala Ser Pro Leu Pro Asp Pro Gly Thr Pro Leu Pro Pro Asp Pro Thr			

Ser Val

Thr Gly Asp Pro Gly Gly Gln Leu Val Leu Ala Gly Asp Pro Arg Gln

65		70		75		80
Leu Gly Pro Val	Leu Arg Ser Pro Leu Thr Gln Lys His Gly Leu Gly					
	85		90		95	
Tyr Ser Leu Leu Glu Arg Leu Leu Thr Tyr Asn Ser Leu Tyr Lys Lys						
	100		105		110	
Gly Pro Asp Gly Tyr Asp Pro Gln Phe Ile Thr Lys Leu Leu Arg Asn						
	115		120		125	
Tyr Arg Ser His Pro Thr Ile Leu Asp Ile Pro Asn Gln Leu Tyr Tyr						
	130		135		140	
Glu Gly Glu Leu Gln Ala Cys Ala Asp Val Val Asp Arg Glu Arg Phe						
	145		150		155	160
Cys Arg Trp Ala Xaa Leu Pro Arg Gln Gly Phe Pro Ile Ile Phe His						
	165		170		175	
Gly Val Met Gly Lys Asp Glu Arg Glu Gly Asn Ser Pro Ser Phe Phe						
	180		185		190	
Asn Pro Glu Glu Ala Ala Thr Val Thr Ser Tyr Leu Lys Leu Leu Leu						
	195		200		205	
Ala Pro Ser Ser Lys Lys Gly Lys Ala Arg Leu Ser Pro Arg Ser Val						
	210		215		220	
Gly Val Ile Ser Pro Tyr Arg Lys Gln Val Glu Lys Ile Arg Tyr Cys						
	225		230		235	240
Ile Thr Lys Leu Asp Arg Glu Leu Arg Gly Leu Asp Asp Ile Lys Asp						
	245		250		255	
Leu Lys Val Gly Ser Val Glu Glu Phe Gln Gly Gln Glu Arg Ser Val						
	260		265		270	
Ile Leu Ile Ser Thr Val Arg Xaa Ala Arg Ala Leu Cys Ser Trp Ile						
	275		280		285	
Trp Thr Leu Ile Trp Val Ser Leu Arg Thr Pro Arg Gly Ser Met						
	290		295		300	

&lt;210&gt; 508

&lt;211&gt; 250

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 508

Glu	Gln	Tyr	Leu	Pro	Leu	Thr	Glu	Glu	Glu	Leu	Glu	Lys	Glu	Ala	Xaa
1				5					10					15	
Lys	Val	Glu	Gly	Phe	Asp	Leu	Val	Gln	Lys	Pro	Ser	Tyr	Tyr	Val	Arg
		20						25					30		
Leu	Gly	Ser	Leu	Ser	Thr	Lys	Leu	His	Ser	Arg	Ala	Tyr	Gln	Gln	Ala
	35						40					45			
Leu	Ser	Arg	Val	Lys	Glu	Ala	Lys	Gln	Lys	Ser	Gln	Gln	Thr	Ile	Ser
	50					55					60				
Gln	Leu	His	Ser	Thr	Val	His	Leu	Ile	Glu	Phe	Ala	Arg	Lys	Asn	Val
65					70					75					80
Tyr	Ser	Ala	Asn	Gln	Lys	Ile	Gln	Asp	Ala	Gln	Asp	Lys	Leu	Tyr	Leu
			85					90						95	
Ser	Trp	Val	Glu	Trp	Lys	Arg	Ser	Ile	Gly	Tyr	Asp	Asp	Thr	Asp	Glu
		100						105						110	
Ser	His	Cys	Ala	Glu	His	Ile	Glu	Ser	Arg	Thr	Leu	Ala	Ile	Ala	Arg
	115						120					125			
Asn	Leu	Thr	Gln	Gln	Leu	Gln	Thr	Thr	Cys	His	Thr	Leu	Leu	Ser	Asn
	130					135					140				
Ile	Gln	Gly	Val	Pro	Gln	Asn	Ile	Gln	Asp	Gln	Ala	Lys	His	Met	Gly
145					150					155				160	
Val	Met	Ala	Gly	Asp	Ile	Tyr	Ser	Val	Phe	Arg	Asn	Ala	Ala	Ser	Phe
			165						170					175	
Lys	Glu	Val	Ser	Asp	Ser	Leu	Leu	Thr	Ser	Ser	Lys	Gly	Gln	Leu	Gln
		180						185						190	
Lys	Met	Lys	Glu	Ser	Leu	Asp	Asp	Val	Met	Asp	Tyr	Leu	Val	Asn	Asn
	195						200					205			
Thr	Pro	Leu	Asn	Trp	Leu	Val	Gly	Pro	Phe	Tyr	Pro	Gln	Leu	Thr	Glu
	210					215					220				
Ser	Gln	Asn	Ala	Gln	Asp	Gln	Gly	Ala	Glu	Met	Asp	Lys	Ser	Ser	Gln
225					230					235					240

465

Glu Thr Gln Arg Ser Glu His Lys Thr His  
                   245                  250

&lt;210&gt; 509

&lt;211&gt; 98

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (97)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 509

His Glu Leu Trp Gly Cys Gly Pro Val Thr Pro Arg Arg Thr Ala Pro  
   1                  5                  10                  15

Ser Gly Trp Ala Gln Ala Pro Leu Ser Asp Thr Ala Gln Val Tyr Met  
                   20                  25                  30

Glu Leu Gln Gly Leu Val Asp Pro Gln Ile Gln Leu Pro Leu Leu Ala  
           35                  40                  45

Ala Arg Ser Thr Ser Cys Arg Ser Ser Leu Ile Ala Ser Gln Pro Gly  
   50                  55                  60

Pro His Gln Lys Gly Arg Gln Gly Leu Arg Gly Asn Lys Ser Phe Leu  
   65                  70                  75                  80

Pro Ser Ser Trp Asn Cys Gln Asn Trp Thr Arg Gln Pro Leu Thr Ser  
                   85                  90                  95

Xaa Ser

&lt;210&gt; 510

&lt;211&gt; 392

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 510

Gly Ala Met Arg Gly Asp Arg Gly Arg Gly Arg Gly Arg Phe Gly  
   1                  5                  10                  15

Ser Arg Gly Gly Pro Gly Gly Gly Phe Arg Pro Phe Val Pro His Ile  
           20                  25                  30





Thr Leu Glu Gln Gln Asp Met Val Cys Tyr Thr Ala Gln Thr Leu Val  
 305 310 315 320

Arg Ile Leu Ser His Gly Gly Phe Arg Lys Ile Leu Gly Gln Glu Gly  
 325 330 335

Asp Ala Ser Tyr Leu Ala Ser Glu Ile Ser Thr Trp Asp Gly Val Ile  
 340 345 350

Val Thr Pro Ser Glu Lys Ala Tyr Glu Lys Pro Pro Glu Lys Lys Glu  
 355 360 365

Gly Glu Glu Glu Glu Glu Asn Thr Glu Glu Pro Pro Gln Gly Glu Glu  
 370 375 380

Glu Glu Ser Met Glu Thr Gln Glu  
 385 390

<210> 511

<211> 72

<212> PRT

<213> Homo sapiens

<400> 511

His Gly Gly Gly Lys Gly Arg Gln Val Gly Leu His Ser Val Gln Arg  
 1 5 10 15

Pro Ala Arg Arg Glu Thr Ala Ala Ser Trp Gly Leu Cys Val Lys Ile  
 20 25 30

Pro Asp Leu Gly Val Ala Phe Val Tyr Lys Met Gln Glu Gly Lys Pro  
 35 40 45

Val Pro Asp Ser Ser Arg Gln His Ala Gln Leu Ser Gly Ser Pro Val  
 50 55 60

Ser Gln Gly Leu Ser Leu Pro Leu  
 65 70

<210> 512

<211> 181

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 512

Gly Trp Cys Ser Cys Ala His Ser Ser Ala Trp Pro Gly Xaa Trp Gly

1 5 10 15

Ala Ser Gly Ile Pro Gln Gln Ala Pro Met Thr Val Cys Asp Gln Ala

20 25 30

Xaa Pro Val Thr Phe Leu Leu Leu His Leu Glu Gly Gly Asp Ile His

35 40 45

Thr Val Ser His Leu Ser Ser Pro Pro Pro Gly Val Ala His Arg Met

50 55 60

Gly Thr Gly Gly Ser Arg Asn Pro Asn Pro Ala Trp Leu Gly Gly Ala

65 70 75 80

Leu Leu Val Arg Gly Arg Pro Ala Ser Leu Ala Pro Trp Gly His Ser

85 90 95

Trp Lys Arg Gly Leu Ala His Ala Pro Leu Arg Ala Gly Thr Cys Thr

100 105 110

Gly His Thr Arg His Ser Ala Cys Trp Asn Arg Trp Leu Cys Ser Cys

115 120 125

Ser Gly Pro Arg Ala Ala Xaa Leu Arg Pro Cys Thr Ser His Met His

130 135 140

Trp Thr Arg Ala Glu Thr Pro Val Cys Tyr Arg Ala Leu Val Leu Cys

145 150 155 160

Gly Pro Gly Ala Thr Ala Gln Ser Ser Gln Trp Arg Ser Thr Pro Leu

165 170 175

Asp Ser Ile Phe Phe

180

&lt;210&gt; 513

&lt;211&gt; 202

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 513

Leu Gly Asp Thr Ile Glu Gly Thr Pro Ala Gly Thr Val Pro Xaa Phe  
 1 5 10 15

Pro Gly Arg Pro Thr Arg Ala Ile Met Ala Gln Asp Gln Gly Glu Lys  
 20 25 30

Glu Asn Pro Met Arg Glu Leu Arg Ile Arg Lys Leu Cys Leu Asn Ile  
 35 40 45

Cys Val Gly Glu Ser Gly Asp Arg Leu Thr Arg Ala Ala Lys Val Leu  
 50 55 60

Glu Gln Leu Thr Gly Gln Thr Pro Val Phe Ser Lys Ala Arg Tyr Thr  
 65 70 75 80

Val Arg Ser Phe Gly Ile Arg Arg Asn Glu Lys Ile Ala Val His Cys  
 85 90 95

Thr Val Arg Gly Ala Lys Ala Glu Glu Ile Leu Glu Lys Gly Leu Lys  
 100 105 110

Val Arg Glu Tyr Glu Leu Arg Lys Asn Asn Phe Ser Asp Thr Gly Asn  
 115 120 125

Phe Gly Phe Gly Ile Gln Glu His Ile Asp Leu Gly Ile Lys Tyr Asp  
 130 135 140

Pro Ser Ile Gly Ile Tyr Gly Leu Asp Phe Tyr Val Val Leu Gly Arg  
 145 150 155 160

Pro Gly Phe Ser Ile Ala Asp Lys Lys Arg Arg Thr Gly Cys Ile Gly  
 165 170 175

Ala Lys His Arg Ile Ser Lys Glu Glu Ala Met Arg Trp Phe Gln Gln  
 180 185 190

Lys Tyr Asp Gly Ile Ile Leu Pro Gly Lys  
 195 200

<210> 514  
<211> 63  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (1)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (2)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (5)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (16)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (35)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 514  
Xaa Xaa Lys Asn Xaa Ile Thr Pro Lys Glu Glu Ser Pro Pro His Xaa  
1 5 10 15  
Ala Leu Leu Ser Lys Cys Leu Leu Thr Pro Ser Pro Lys Met Pro Pro  
20 25 30  
Ile Leu Xaa Val Met Ala Ala Leu Gly Phe Glu Arg Arg Glu Phe Gly  
35 40 45  
Ser Thr Ser Val Glu Arg Val Gln Ser Arg Gln Leu Asp Cys Phe  
50 55 60

<210> 515  
<211> 218  
<212> PRT  
<213> Homo sapiens

<220>  
 <221> SITE  
 <222> (151)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (209)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (211)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 515  
 Ser Leu Ala Arg Gly Cys Gln Arg Pro Asp Ala Val Leu Tyr Ala Arg  
 1 5 10 15  
 His Tyr Asn Ile Pro Val Ile His Ala Phe Arg Arg Ala Val Asp Asp  
 20 25 30  
 Pro Gly Leu Val Phe Asn Gln Leu Pro Lys Met Leu Tyr Pro Glu Tyr  
 35 40 45  
 His Lys Val His Gln Met Met Arg Glu Gln Ser Ile Leu Ser Pro Ser  
 50 55 60  
 Pro Tyr Glu Gly Tyr Arg Ser Leu Pro Arg His Gln Leu Leu Cys Phe  
 65 70 75 80  
 Lys Glu Asp Cys Gln Ala Val Phe Gln Asp Leu Glu Gly Val Glu Lys  
 85 90 95  
 Val Phe Gly Val Ser Leu Val Leu Val Leu Ile Gly Ser His Pro Asp  
 100 105 110  
 Leu Ser Phe Leu Pro Gly Ala Gly Ala Asp Phe Ala Val Asp Pro Asp  
 115 120 125  
 Gln Pro Leu Ser Ala Lys Arg Asn Pro Ile Asp Val Asp Pro Phe Thr  
 130 135 140  
 Tyr Gln Ser Thr Arg Gln Xaa Gly Leu Tyr Ala Met Gly Pro Leu Ala  
 145 150 155 160  
 Gly Asp Asn Phe Val Arg Phe Val Gln Gly Gly Ala Leu Ala Val Ala  
 165 170 175  
 Ser Ser Leu Leu Arg Lys Glu Gln Asn His Leu His Arg Gln Pro Trp  
 180 185 190

Ser Ser Leu Arg Gly Ile His Pro Leu Ile Asp Leu Lys Ser Gly Val  
195 200 205

Xaa Pro Xaa Leu Val Lys Leu Thr Ala Gln  
210 215

<210> 516  
<211> 41  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (22)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 516  
Asn Gly Arg Pro Asp Ser Thr Gly Pro Ala Ile Pro Gly Ile Leu Ser  
1 5 10 15  
Trp Gly Phe Glu Thr Xaa Leu Arg Asp Arg Glu Thr Asp Pro Arg Asn  
20 25 30

Val Leu Asn Cys Asn Gly Pro His Thr  
35 40

<210> 517  
<211> 250  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (118)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (161)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (204)  
<223> Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 517

Gly Phe Asn Arg Ser Phe Cys Gly Arg Asn Ala Thr Val Tyr Gly Lys  
1 5 10 15

Gly Val Tyr Phe Ala Arg Arg Ala Ser Leu Ser Val Gln Asp Arg Tyr  
20 25 30

Ser Pro Pro Asn Ala Asp Gly His Lys Ala Val Phe Val Ala Arg Val  
35 40 45

Leu Thr Gly Asp Tyr Gly Gln Gly Arg Arg Gly Leu Arg Ala Pro Pro  
50 55 60

Leu Arg Gly Pro Gly His Val Leu Leu Arg Tyr Asp Ser Ala Val Asp  
65 70 75 80

Cys Ile Cys Gln Pro Ser Ile Phe Val Ile Phe His Asp Thr Gln Ala  
85 90 95

Leu Pro Thr His Leu Ile Thr Cys Glu Ala Arg Ala Pro Arg Phe Pro  
100 105 110

Arg Arg Pro Leu Trp Xaa Pro Gly Pro Leu Pro Arg His Leu Thr Glu  
115 120 125

Gly Ala Thr Leu Trp Pro Pro Ala Ser Gln Ala Pro Ser Ser Ala Gln  
130 135 140

Ala Asp Ala Pro Arg Pro Gln Leu Trp Pro Pro Glu Leu Ser Pro Gly  
145 150 155 160

Xaa Pro Cys Leu Pro Leu Arg Ala Pro Glu Gly Gly Val Gly Asp Gly  
165 170 175

Gly Gln Gln Arg Pro Arg Gly Ala Gly Leu Gly Pro Ser Leu Gly Arg  
180 185 190

Pro His His Gln Gly Ser Ala Glu Pro Arg Arg Xaa His Arg Pro Pro  
195 200 205

Ala Ala Pro Arg Pro Arg Pro Ser Arg Leu Cys Cys Leu Asn Lys Arg  
210 215 220

Glu Arg Glu Pro Arg Arg Lys Gly Pro Gly Lys Lys Lys Lys Lys  
225 230 235 240

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys  
245 250

<210> 518  
 <211> 100  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (3)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (7)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 518  
 Asn Pro Xaa Lys Lys Leu Xaa Ile Leu Ile Lys Trp Pro Pro Pro Phe  
           1                  5                  10                  15  
 Pro Pro Ser Phe Pro Pro Ser Pro Asn Ser Leu Ser Ser Ser Ser Phe  
                   20                  25                  30  
 Pro Pro Pro Leu Ser Leu Phe Ser Pro Ser Phe Thr Phe Leu Ile Ser  
           35                  40                  45  
 Val Lys Leu Glu Arg Phe Glu Ile Pro Ile Lys Val Arg Leu Ser Pro  
           50                  55                  60  
 Glu Pro Trp Thr Pro Glu Thr Gly Leu Val Thr Asp Ala Phe Lys Leu  
           65                  70                  75                  80  
 Lys Arg Lys Glu Leu Arg Asn His Tyr Leu Lys Asp Ile Glu Arg Met  
                   85                  90                  95  
 Tyr Gly Gly Lys  
                   100

<210> 519  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (5)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE



&lt;222&gt; (17)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 519

His Glu Asp Gly Xaa Leu Met Gly Cys Arg His Arg Trp His Pro Arg  
 1 5 10 15

Xaa Val Pro Phe His Gln Thr Ser Pro Lys Thr Glu Leu Glu Ser Thr  
 20 25 30

Ile Phe Gly Ser Pro Arg Leu Ala Ser Gly Leu Phe Pro Glu Trp Gln  
 35 40 45

Ser Trp Gly Arg Met Glu Asn Leu Ala Ser Tyr Arg  
 50 55 60

&lt;210&gt; 520

&lt;211&gt; 120

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (25)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 520

Ser His Pro Tyr Ala Pro Ser Cys Gly Leu Arg Gly Pro Gly Ala Ala  
 1 5 10 15

Ser Arg Ala Arg Thr Arg Glu Arg Xaa Pro Gln Ala Glu Ala Glu Ala  
 20 25 30

Arg Ser Thr Pro Gly Pro Ala Gly Ser Arg Leu Gly Pro Glu Thr Phe  
 35 40 45

Arg Gln Arg Phe Arg Gln Phe Arg Tyr Gln Asp Ala Ala Gly Pro Arg  
 50 55 60

Glu Ala Phe Arg Gln Leu Arg Glu Leu Ser Arg Gln Trp Leu Arg Pro  
 65 70 75 80

Asp Ile Arg Thr Lys Glu Gln Ile Val Glu Met Leu Val Gln Glu Gln  
 85 90 95

Leu Leu Ala Ile Leu Pro Glu Ala Ala Arg Ala Arg Arg Ile Arg Arg  
 100 105 110

Arg Thr Asp Val Arg Ile Thr Gly

476

115

120

<210> 521  
 <211> 96  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 521

Gly His Gln Thr Val Ser Pro Ser Thr Gly Ser Arg Val Thr Arg Met  
 1 5 10 15

Phe Ser Leu Ile Ser Phe Ser His Val Phe Ile Lys Asp Ile Cys Lys  
 20 25 30

Leu Pro Lys Asp Glu Gly Thr Cys Arg Asp Phe Ile Leu Lys Trp Tyr  
 35 40 45

Tyr Asp Pro Asn Thr Lys Ser Cys Ala Arg Phe Trp Tyr Gly Gly Cys  
 50 55 60

Gly Gly Asn Glu Asn Lys Phe Gly Ser Gln Lys Glu Cys Glu Lys Val  
 65 70 75 80

Cys Ala Pro Val Leu Ala Lys Pro Gly Val Ile Ser Val Met Gly Thr  
 85 90 95

<210> 522  
 <211> 122  
 <212> PRT  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (18)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 522

Asn Ser Gly Phe Arg Pro Lys Asn Pro Val Gly Arg Gly Gly Glu Pro  
 1 5 10 15

Glu Xaa Cys Gly Gly Ala Gly Gly Leu Gly Cys Thr Leu Val Trp Gly  
 20 25 30

Gly Thr Gly Ala Ala Val Val Thr Gly Val Val Trp Leu Leu Leu Pro

35                      40                      45  
 Asn Gly Gly Val Gly Val Gly Leu Leu Gly Pro Gln Ser Pro Val Gly  
     50                      55                      60  
 Gly Ser Asp Ser Ala Pro Tyr Ser Leu His Pro Ala Gly Arg Thr Trp  
     65                      70                      75                      80  
 Gly Leu Arg Ser Glu Cys Ile Pro Pro Leu Ser Phe Asn Leu Ser Cys  
                     85                      90                      95  
 Arg Thr His Ser Gly Pro Gly Ala Arg Leu Gly Glu Ala Gly Pro Asn  
                     100                      105                      110  
 Tyr Gly Ser Arg Glu Leu Gln Val Pro Thr  
     115                      120

<210> 523  
 <211> 94  
 <212> PRT  
 <213> Homo sapiens

<400> 523  
 Leu Ile Pro Gln Val Cys Cys Lys His Ser Met Glu Asp Thr Asp Asp  
     1                      5                      10                      15  
 Ser Leu Val Leu Val Phe Leu Ser Ala Val Asn Val Gln Gln Phe Ala  
                     20                      25                      30  
 Gln Glu Leu Gly Asp His Ile Cys Leu Ser Gly Gln Gly Ser Glu Val  
                     35                      40                      45  
 His Trp Asn Leu Leu Arg Asn Leu Phe Val Lys Thr Ile Val Asn Asn  
                     50                      55                      60  
 Tyr Cys Ile Phe Leu Gln Lys Tyr Ile Leu Glu Asn Cys Ile Leu Ser  
     65                      70                      75                      80  
 Ile Lys Val Phe Leu Cys Lys Lys Lys Lys Lys Lys Leu Val  
                     85                      90

<210> 524  
 <211> 93  
 <212> PRT  
 <213> Homo sapiens

<220>

<221> SITE  
 <222> (78)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (86)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (93)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 524  
 Ser Ala Val Met Gly Arg Lys Lys Lys Lys Gln Leu Lys Pro Trp Cys  
   1                  5                  10                  15  
  
 Trp Tyr Cys Asn Arg Asp Phe Asp Asp Glu Lys Ile Leu Ile Gln His  
                   20                  25                  30  
  
 Gln Lys Ala Lys His Phe Lys Cys His Ile Cys His Lys Lys Leu Tyr  
           35                  40                  45  
  
 Thr Gly Pro Gly Leu Ala Ile His Cys Met Gln Val His Lys Glu Thr  
   50                  55                  60  
  
 Ile Asp Ala Val Pro Asn Ala Tyr Leu Gly Glu Gln Thr Xaa Ile Gly  
   65                  70                  75                  80  
  
 Asn Ile Trp Tyr Gly Xaa Tyr Ser Arg Lys Arg Tyr Xaa  
                   85                  90

<210> 525  
 <211> 324  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (323)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 525  
 Asp Leu Arg Leu Ser Arg Pro Glu Ala Val Glu Ala Glu Ala Met Met  
   1                  5                  10                  15  
  
 Ala Ala Met Ala Thr Ala Arg Val Arg Met Gly Pro Arg Cys Ala Gln  
           20                  25                  30

Ala Leu Trp Arg Met Pro Trp Leu Pro Val Phe Leu Ser Leu Ala Ala  
 35 40 45  
 Ala Ala Ala Ala Ala Ala Glu Gln Gln Val Pro Leu Val Leu Trp  
 50 55 60  
 Ser Ser Asp Arg Asp Leu Trp Ala Pro Ala Ala Asp Thr His Glu Gly  
 65 70 75 80  
 His Ile Thr Ser Asp Leu Gln Leu Ser Thr Tyr Leu Asp Pro Ala Leu  
 85 90 95  
 Glu Leu Gly Pro Arg Asn Val Leu Leu Phe Leu Gln Asp Lys Leu Ser  
 100 105 110  
 Ile Glu Asp Phe Thr Ala Tyr Gly Gly Val Phe Gly Asn Lys Gln Asp  
 115 120 125  
 Ser Ala Phe Ser Asn Leu Glu Asn Ala Leu Asp Leu Ala Pro Ser Ser  
 130 135 140  
 Leu Val Leu Pro Ala Val Asp Trp Tyr Ala Val Ser Thr Leu Thr Thr  
 145 150 155 160  
 Tyr Leu Gln Glu Lys Leu Gly Ala Ser Pro Leu His Val Asp Leu Ala  
 165 170 175  
 Thr Leu Arg Glu Leu Lys Leu Asn Ala Ser Leu Pro Ala Leu Leu Leu  
 180 185 190  
 Ile Arg Leu Pro Tyr Thr Ala Ser Ser Gly Leu Met Ala Pro Arg Glu  
 195 200 205  
 Val Leu Thr Gly Asn Asp Glu Val Ile Gly Gln Val Leu Ser Thr Leu  
 210 215 220  
 Lys Ser Glu Asp Val Pro Tyr Thr Ala Ala Leu Thr Ala Val Arg Pro  
 225 230 235 240  
 Ser Arg Val Ala Arg Asp Val Ala Val Val Ala Gly Gly Leu Gly Arg  
 245 250 255  
 Gln Leu Leu Gln Lys Gln Pro Val Ser Pro Val Ile His Pro Pro Val  
 260 265 270  
 Ser Tyr Asn Asp Thr Ala Pro Arg Ile Leu Phe Trp Ala Gln Asn Phe  
 275 280 285  
 Ser Val Ala Tyr Lys Asp Gln Trp Glu Asp Leu Thr Pro Leu Thr Phe  
 290 295 300

Gly Val Gln Glu Leu Asn Leu Thr Gly Ser Phe Trp Asn Asp Ser Phe  
 305 310 315 320

Ala Ser Xaa His

<210> 526

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 526

Phe Xaa Val Ser Trp Thr Trp Lys Gln Val Ser Glu Phe Pro Gly Asp  
 1 5 10 15

Gln Arg Asp Glu Val Leu Gln Leu Pro Pro Ser Ser Cys Asn Leu Val  
 20 25 30

Ser Ser Gly Ala Gly Gly Glu Pro Glu Lys Leu Ala Ser Tyr Ile Thr  
 35 40 45

Ser Leu Trp Leu Phe Phe Ile Cys Lys Thr Arg Ile Ile Leu Asn Cys  
 50 55 60

Lys Gly  
 65

<210> 527

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 527

Asn Thr Gln Leu Trp Phe Leu Cys Phe Pro Asn Cys Lys Ala Ala Asp  
 1 5 10 15

Asn Lys Thr Pro Gly Phe His Val Ser Ser Ala Met Ser Thr Leu Thr  
                   20                  25                  30

Gln Ile Leu Lys Gln Asn Ser Xaa Asn Ala Val Leu Arg Ile Gln Leu  
                   35                  40                  45

Leu Leu Lys Pro Ile Ser Ile Cys Ile Ile Thr Thr Asn Ile  
                   50                  55                  60

<210> 528

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (104)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 528

Tyr Asn Lys Ile Glu Ile Met His Leu Val Met Trp Pro Thr Ser Leu  
           1                  5                  10                  15

Leu Thr Thr Met Asp Cys Phe Gln Gln Gln Leu Ile Phe Trp Ser Val  
                   20                  25                  30

Leu Arg Gly Ala Cys Met Ser Phe Val Thr Ser Gly Ser Thr Pro Ala  
                   35                  40                  45

Val Lys Tyr Cys Phe His Leu Pro Leu Gln Lys Ala Ser Cys Leu Leu  
                   50                  55                  60

Thr Ser Thr Ala Lys Ala Leu Phe Trp Thr Gly Tyr Leu Ile Lys Xaa  
           65                  70                  75                  80

Ile Ser Val Arg Leu Cys Ser Val Ile Pro Ser Glu Pro Arg Phe Val  
                   85                  90                  95

Ser Lys Ala Thr Val Leu Ser Xaa Xaa Pro Cys Val Trp Gly Gln Val

482

100 105 110  
 Ala Ile Pro Pro Met Ser Leu Val Ile Leu  
 115 120  
  
 <210> 529  
 <211> 182  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (25)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 529  
 Asp Arg Thr Arg Leu Ser Gln Ala Ser Thr Pro Thr Pro Val Cys Trp  
 1 5 10 15  
 Gly Leu Leu Gln Pro Pro Pro Trp Xaa Glu Ala Trp Tyr Arg Leu Thr  
 20 25 30  
 His Arg Gly Leu Cys Gln Val Arg Phe Cys Arg Trp Ser Gln Ala Leu  
 35 40 45  
 Pro Glu Ala Arg Gly Gly Ala Trp Ala Gly Ser Pro Gly Glu Gly Gln  
 50 55 60  
 Ala Gly Pro Arg Leu His Thr His Ile Gln Pro Ala Gly Leu Ser Ala  
 65 70 75 80  
 Val Leu Ser Pro Ser Leu Ser Ser Pro Ser Ser Ala Val Thr Leu Ser  
 85 90 95  
 Ser Pro Ser Leu Pro Ala Ser Pro Pro Ala Ala Pro Pro Val Lys Arg  
 100 105 110  
 Met Thr Lys Asp Leu Ser Tyr Ala Gly Ser Lys Asn Gln Asn Phe Leu  
 115 120 125  
 Leu Ala Phe Ser Phe Val Ala Ser Pro Ala Pro Ala Leu Pro Val Ser  
 130 135 140  
 His Pro Gly Pro Arg Leu Glu Ala Ser Leu His Leu Ser Tyr Cys Phe  
 145 150 155 160  
 Lys Pro Lys Phe Thr Val Ser Val Gly Gly Gln Asp Leu Leu Ser Pro  
 165 170 175



Pro Leu Leu His Pro Pro  
180

<210> 530  
<211> 183  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (6)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (79)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (80)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (81)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 530  
Ala Leu Val Leu Gly Xaa Lys Ser Val Arg Met Ala Ser Ser Arg Met  
1 5 10 15

Thr Arg Arg Asp Pro Leu Thr Asn Lys Val Ala Leu Val Thr Ala Ser  
20 25 30

Thr Asp Gly Ile Gly Phe Ala Ser Pro Gly Val Trp Pro Arg Thr Gly  
35 40 45

Pro Arg Gly Arg Gln Gln Pro Glu Ala Ala Glu Cys Gly Pro Gly Gly  
50 55 60

Gly Thr Leu Gln Gly Glu Gly Leu Ser Val Thr Gly Thr Cys Xaa Xaa  
65 70 75 80

Xaa Gly Lys Ala Glu Asp Arg Glu Arg Leu Val Ala Thr Ala Val Lys  
85 90 95

Leu His Gly Gly Ile Asp Ile Leu Val Ser Asn Ala Ala Val Asn Pro  
100 105 110

484

Phe Phe Gly Ser Ile Met Asp Val Thr Glu Glu Val Trp Asp Lys Leu  
 115 120 125

Trp Met Asp Lys Glu Lys Glu Glu Ser Met Lys Glu Thr Leu Arg Ile  
 130 135 140

Arg Arg Leu Gly Glu Pro Glu Asp Cys Ala Gly Ile Val Ser Phe Leu  
 145 150 155 160

Cys Ser Glu Asp Ala Ser Tyr Ile Thr Gly Glu Thr Val Val Val Gly  
 165 170 175

Gly Gly Thr Pro Ser Arg Leu  
 180

&lt;210&gt; 531

&lt;211&gt; 129

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (89)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (103)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 531

Asn Ser Ala Pro Leu Ser Pro Thr Gly Leu Gly Gln Gly His Thr Gly  
 1 5 10 15

His Val Arg Phe Leu Ala Ala Val Gln Leu Pro Asp Gly Phe Asn Leu  
 20 25 30

Leu Cys Pro Thr Pro Pro Pro Pro Pro Asp Thr Gly Pro Glu Lys Leu  
 35 40 45

Pro Ser Leu Glu His Arg Asp Ser Pro Trp His Arg Gly Pro Ala Pro  
 50 55 60

Ala Arg Pro Lys Met Leu Val Ile Ser Gly Gly Asp Gly Tyr Glu Asp  
 65 70 75 80

Phe Arg Leu Ser Ser Gly Gly Gly Xaa Ala Val Arg Leu Trp Val Glu  
 85 90 95

485

Thr Thr Ala Gln Thr Thr Xaa Ser Cys Gly Gly Cys Asp Pro Val Cys  
 100 105 110

Arg Gly Pro Gly Leu Ala Arg Pro Pro Ala Phe Ser Leu Leu Ala Ser  
 115 120 125

Pro

<210> 532  
 <211> 91  
 <212> PRT  
 <213> Homo sapiens

<400> 532  
 Gly Ala Ile Ala Ser Ser Gly Pro Thr Gly Gly Arg Val Arg Lys His  
 1 5 10 15  
 Gln Leu Leu Pro Gly Ala Val Arg Glu Trp Glu Gln Leu Trp Ala Pro  
 20 25 30  
 His Phe Arg Gln Val Leu Pro Lys Pro Ser Asp Ala Val Arg Pro Gly  
 35 40 45  
 Leu Pro Val Val Leu Phe Arg Leu Cys Phe Gln Asn Ala Phe Ile Ser  
 50 55 60  
 Ser Val Pro Phe Gly Pro His Lys Ser Pro Trp Gly Val Gly Gly Gly  
 65 70 75 80  
 Leu Cys Arg His Pro His Phe Lys Ala Gly Ser  
 85 90

<210> 533  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (63)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 533  
 Asn Leu Cys Gln Val Gln Pro Thr Arg Leu Tyr Ser Ser Leu His Ser  
 1 5 10 15

Gly Leu His His Val Arg Gln Val Thr Gln Lys Ser Tyr Lys Val Ser  
                   20                                  25                                  30

Thr Ser Gly Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro  
           35                                  40                                  45

Gly Ser Arg Ile Ser Ser Ser Ala Phe Ser Arg Val Gly Gly Xaa Ser  
           50                                  55                                  60

Gly Gly Ala  
       65

<210> 534

<211> 144

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (140)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (141)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 534

Phe Asn Arg Arg Tyr Pro Lys Ile Gln Phe Ser Leu Ser Thr Gly Pro  
       1                                  5                                  10                                  15

Ser Gly Thr Met Leu Asp Gly Val Leu Glu Gly Lys Leu Asn Ala Ala  
           20                                  25                                  30

Phe Ile Asp Gly Pro Ile Asn His Thr Ala Ile Asp Gly Ile Pro Val  
           35                                  40                                  45

Tyr Arg Glu Glu Leu Met Ile Val Thr Pro Gln Gly Tyr Ala Pro Val  
           50                                  55                                  60

Thr Arg Ala Ser Gln Val Asn Gly Ser Asn Ile Tyr Ala Phe Arg Ala  
       65                                  70                                  75                                  80

Asn Cys Ser Tyr Arg Arg His Phe Glu Ser Trp Phe His Ala Asp Gly  
           85                                  90                                  95

Ala Ala Pro Gly Thr Ile His Glu Met Glu Ser Tyr His Gly Met Leu  
           100                                  105                                  110

Ala Cys Val Ile Ala Gly Ala Gly Ile Ala Leu Ile Pro Arg Ser Met  
 115 120 125

Leu Glu Ser Met Pro Gly His His Gln Val Glu Xaa Xaa Ala Val Ser  
 130 135 140

<210> 535  
 <211> 175  
 <212> PRT  
 <213> Homo sapiens

<400> 535  
 Arg Ala Pro Ala Arg Ile Ser Gly Gly Gly Ser Ala Met Val Gly Gly  
 1 5 10 15

Gly Gly Val Gly Gly Gly Leu Leu Glu Asn Ala Asn Pro Leu Ile Tyr  
 20 25 30

Gln Arg Ser Gly Glu Arg Pro Val Thr Ala Gly Glu Glu Asp Glu Gln  
 35 40 45

Val Pro Asp Ser Ile Asp Ala Arg Glu Ile Phe Asp Leu Ile Arg Ser  
 50 55 60

Ile Asn Asp Pro Glu His Pro Leu Thr Leu Glu Glu Leu Asn Val Val  
 65 70 75 80

Glu Gln Val Arg Val Gln Val Ser Asp Pro Glu Ser Thr Val Ala Val  
 85 90 95

Ala Phe Thr Pro Thr Ile Pro His Cys Ser Met Ala Thr Leu Ile Gly  
 100 105 110

Leu Ser Ile Lys Val Lys Leu Leu Arg Ser Leu Pro Gln Arg Phe Lys  
 115 120 125

Met Asp Val His Ile Thr Pro Gly Thr His Ala Ser Glu His Ala Val  
 130 135 140

Asn Lys Gln Leu Ala Asp Lys Glu Arg Val Ala Ala Ala Leu Glu Asn  
 145 150 155 160

Thr His Leu Leu Glu Val Val Asn Gln Cys Leu Ser Ala Arg Ser  
 165 170 175

&lt;210&gt; 536

&lt;211&gt; 148

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 536

Gly Trp His Arg Thr His His Arg Gly Arg His Gln Ala Arg Glu Ala  
1 5 10 15

Glu Glu Glu Ala Trp Ala Ala Ala Glu Pro Ile Lys Lys Val Arg Lys  
20 25 30

Ser Leu Ala Leu Asp Ile Val Asp Glu Asp Val Lys Leu Met Met Ser  
35 40 45

Thr Leu Pro Lys Ser Leu Ser Leu Pro Thr Thr Ala Pro Ser Asn Ser  
50 55 60

Ser Ser Leu Thr Leu Ser Gly Ile Lys Glu Asp Asn Ser Leu Leu Asn  
65 70 75 80

Gln Gly Phe Leu Gln Ala Lys Pro Glu Lys Ala Ala Val Ala Gln Lys  
85 90 95

Pro Arg Ser His Phe Thr Thr Pro Ala Pro Met Ser Ser Ala Trp Lys  
100 105 110

Thr Val Ala Cys Gly Gly Thr Arg Asp Gln Leu Phe Met Gln Glu Lys  
115 120 125

Ala Arg Gln Leu Leu Gly Arg Leu Lys Pro Ser His Thr Ser Arg Thr  
130 135 140

Leu Ile Leu Ser  
145

&lt;210&gt; 537

&lt;211&gt; 70

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 537

Arg Pro Thr Arg Ser Ala Trp Trp Gly Arg Leu Leu Ser Arg Val Ser  
 1 5 10 15

Pro Gln Pro Arg Pro Ala Ser Pro Ser Val Ser Thr Arg Asn Gln Leu  
 20 25 30

Pro Glu Ala Arg Arg Gly Val Glu Xaa Xaa Glu Cys Glu Glu Thr Ala  
 35 40 45

Ala Ser Ala Glu Arg Ala Gly Pro Pro Arg Ala Leu Val Phe Gly Ala  
 50 55 60

Gln Ser Arg Ser Pro Gly  
 65 70

&lt;210&gt; 538

&lt;211&gt; 206

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 538

Gly Glu Val Ser Ala Ser Gly Ile Ala Arg Arg Gly Gly Pro Met Ala  
 1 5 10 15

Pro Leu Gly Gly Ala Pro Arg Leu Val Leu Leu Phe Ser Gly Lys Arg  
 20 25 30

Lys Ser Gly Lys Asp Phe Val Thr Glu Ala Leu Gln Ser Arg Leu Gly  
 35 40 45

Ala Asp Val Cys Ala Val Leu Arg Leu Ser Gly Pro Leu Lys Glu Gln  
 50 55 60

Tyr Ala Gln Glu His Gly Leu Asn Phe Gln Arg Leu Leu Asp Thr Ser  
 65 70 75 80

Thr Tyr Lys Glu Ala Phe Arg Lys Asp Met Ile Arg Trp Gly Glu Glu  
 85 90 95

Lys Arg Gln Ala Asp Pro Gly Phe Phe Cys Arg Lys Ile Val Glu Gly  
 100 105 110

Ile Ser Gln Pro Ile Trp Leu Val Ser Asp Thr Arg Arg Val Ser Asp  
 115 120 125

490

Ile Gln Trp Phe Arg Glu Ala Tyr Gly Ala Val Thr Gln Thr Val Arg  
 130 135 140

Val Val Ala Leu Glu Gln Ser Arg Gln Gln Arg Gly Trp Val Phe Thr  
 145 150 155 160

Pro Gly Val Asp Asp Ala Glu Ser Glu Cys Gly Leu Asp Asn Phe Gly  
 165 170 175

Asp Phe Asp Trp Val Ile Glu Asn His Gly Val Glu Gln Arg Leu Glu  
 180 185 190

Glu Gln Leu Glu Asn Leu Ile Glu Phe Ile Arg Ser Arg Leu  
 195 200 205

&lt;210&gt; 539

&lt;211&gt; 350

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 539

Ser Thr Leu Ile Ala Phe Ile Val Ile Ser Thr Leu Phe Pro Leu Leu  
 1 5 10 15

Asp Met Thr Glu Ile Tyr Phe Ser Leu Leu Asp Glu Ile Val Asp Thr  
 20 25 30

Leu Gly Glu Gly Ala Phe Gly Lys Val Val Glu Cys Ile Asp His Lys  
 35 40 45

Ala Gly Gly Arg His Val Ala Val Lys Ile Val Lys Asn Val Asp Arg  
 50 55 60

Tyr Cys Glu Ala Ala Arg Ser Glu Ile Gln Val Leu Glu His Leu Asn  
 65 70 75 80

Thr Thr Asp Pro Asn Ser Thr Phe Arg Cys Val Gln Met Leu Glu Trp  
 85 90 95

Phe Glu His His Gly His Ile Cys Ile Val Phe Glu Leu Leu Gly Leu  
 100 105 110

Ser Thr Tyr Asp Phe Ile Lys Glu Asn Gly Phe Leu Pro Phe Arg Leu  
 115 120 125

Asp His Ile Arg Lys Met Ala Tyr Gln Ile Cys Lys Ser Val Asn Phe  
 130 135 140



Leu His Ser Asn Lys Leu Thr His Thr Asp Leu Lys Pro Glu Asn Ile  
 145 150 155 160

Leu Phe Val Gln Ser Asp Tyr Thr Glu Ala Tyr Asn Pro Lys Ile Lys  
 165 170 175

Arg Asp Glu Arg Thr Leu Ile Asn Pro Asp Ile Lys Val Val Asp Phe  
 180 185 190

Gly Ser Ala Thr Tyr Asp Asp Glu His His Ser Thr Leu Val Ser Thr  
 195 200 205

Arg His Tyr Arg Ala Pro Glu Val Ile Leu Ala Leu Gly Trp Ser Gln  
 210 215 220

Pro Cys Asp Val Trp Ser Ile Gly Cys Ile Leu Ile Glu Tyr Tyr Leu  
 225 230 235 240

Gly Phe Thr Val Phe Pro Thr His Asp Ser Lys Glu His Leu Ala Met  
 245 250 255

Met Glu Arg Ile Leu Gly Pro Leu Pro Lys His Met Ile Gln Lys Thr  
 260 265 270

Arg Lys Arg Lys Tyr Phe His His Asp Arg Leu Asp Trp Asp Glu His  
 275 280 285

Ser Ser Ala Gly Arg Tyr Val Ser Arg Arg Cys Lys Pro Leu Lys Glu  
 290 295 300

Phe Met Leu Ser Gln Asp Val Glu His Glu Arg Leu Phe Asp Leu Ile  
 305 310 315 320

Gln Lys Met Leu Glu Tyr Asp Pro Ala Lys Arg Ile Thr Leu Arg Glu  
 325 330 335

Ala Leu Lys His Pro Phe Phe Asp Leu Leu Lys Lys Ser Ile  
 340 345 350

<210> 540

<211> 324

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (297)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (304)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (305)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (317)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (321)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 540  
 Gln Ala Thr Met Gly Asn Val Leu Ala Ala Ser Ser Pro Pro Ala Gly  
   1                  5                  10                  15  
 Pro Pro Pro Pro Pro Ala Pro Ala Leu Val Gly Leu Pro Pro Pro Pro  
                   20                  25                  30  
 Pro Ser Pro Pro Gly Phe Thr Leu Pro Pro Leu Gly Gly Ser Leu Gly  
           35                  40                  45  
 Ala Gly Thr Ser Thr Xaa Arg Xaa Ser Glu Arg Thr Pro Gly Ala Ala  
   50                  55                  60  
 Thr Ala Ser Ala Ser Gly Ala Ala Glu Asp Gly Ala Cys Gly Cys Leu  
   65                  70                  75                  80  
 Pro Asn Pro Gly Thr Phe Glu Glu Cys His Arg Lys Cys Lys Glu Leu  
           85                  90                  95  
 Phe Pro Ile Gln Met Glu Gly Val Lys Leu Thr Val Asn Lys Gly Leu  
   100                  105                  110

Ser Asn His Phe Gln Val Asn His Thr Val Ala Leu Ser Thr Ile Gly  
 115 120 125  
 Glu Ser Asn Tyr His Phe Gly Val Thr Tyr Val Gly Thr Lys Gln Leu  
 130 135 140  
 Ser Pro Thr Glu Ala Phe Pro Val Leu Val Gly Asp Met Asp Asn Ser  
 145 150 155 160  
 Gly Ser Leu Asn Ala Gln Val Ile His Gln Leu Gly Pro Gly Leu Arg  
 165 170 175  
 Ser Lys Met Ala Ile Gln Thr Gln Gln Ser Lys Phe Val Asn Trp Gln  
 180 185 190  
 Val Asp Gly Glu Tyr Arg Gly Ser Asp Phe Thr Ala Ala Val Thr Leu  
 195 200 205  
 Gly Asn Pro Asp Val Leu Val Gly Ser Gly Ile Leu Val Ala His Tyr  
 210 215 220  
 Leu Gln Ser Ile Thr Pro Cys Leu Ala Leu Gly Gly Glu Leu Val Tyr  
 225 230 235 240  
 His Arg Arg Pro Gly Glu Glu Gly Thr Val Met Ser Leu Ala Gly Lys  
 245 250 255  
 Tyr Thr Leu Asn Asn Trp Leu Ala Thr Val Thr Leu Gly Gln Ala Gly  
 260 265 270  
 Met His Ala Thr Tyr Tyr His Lys Ala Ser Asp Gln Leu Gln Val Gly  
 275 280 285  
 Val Glu Phe Glu Ala Ser Thr Arg Xaa Gln Asp Thr Ser Val Ser Xaa  
 290 295 300  
 Xaa Val Pro Ala Trp Asn Leu Pro Lys Gly Gln Pro Xaa Leu Ser Lys  
 305 310 315 320  
 Xaa Leu Leu Gly

&lt;210&gt; 541

&lt;211&gt; 204

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 541

Arg Gly Pro Thr Phe Thr Pro Glu Ile Met Ala Ala Glu Asp Val Val  
 1 5 10 15  
 Ala Thr Gly Ala Asp Pro Ser Asp Leu Glu Ser Gly Gly Leu Leu His  
 20 25 30  
 Glu Ile Phe Thr Ser Pro Leu Asn Leu Leu Leu Gly Leu Cys Ile  
 35 40 45  
 Phe Leu Leu Tyr Lys Ile Val Arg Gly Asp Gln Pro Ala Ala Ser Gly  
 50 55 60  
 Asp Ser Asp Asp Asp Glu Pro Pro Pro Leu Pro Arg Leu Lys Arg Arg  
 65 70 75 80  
 Asp Phe Thr Pro Ala Glu Leu Arg Arg Phe Asp Gly Val Gln Asp Pro  
 85 90 95  
 Arg Ile Leu Met Ala Ile Asn Gly Lys Val Phe Asp Val Thr Lys Gly  
 100 105 110  
 Arg Lys Phe Tyr Gly Pro Glu Gly Pro Tyr Gly Val Phe Ala Gly Arg  
 115 120 125  
 Asp Ala Ser Arg Gly Leu Ala Thr Phe Cys Leu Asp Lys Glu Ala Leu  
 130 135 140  
 Lys Asp Glu Tyr Asp Asp Leu Ser Asp Leu Thr Ala Ala Gln Gln Glu  
 145 150 155 160  
 Thr Leu Ser Asp Trp Glu Ser Gln Phe Thr Phe Lys Tyr His His Val  
 165 170 175  
 Gly Lys Leu Leu Lys Glu Gly Glu Glu Pro Thr Val Tyr Ser Asp Glu  
 180 185 190  
 Glu Glu Pro Lys Asp Glu Ser Ala Arg Lys Asn Asp  
 195 200

&lt;210&gt; 542

&lt;211&gt; 193

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (183)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 542

Pro Ala Tyr Ser Leu Gly Leu Leu Lys Ser Val Leu Asp Gly Gly Gly  
 1 5 10 15  
 Ala Gly Ala His Gln Ala Arg Ser Asn Pro Ser Cys Met Tyr Pro Gln  
 20 25 30  
 Gly Thr Phe Val Ile Pro Leu Leu Val Thr Ala His Arg Asp Pro Thr  
 35 40 45  
 Gln Phe Lys Asp Pro Asp Cys Phe Asn Pro Thr Asn Phe Leu Asp Lys  
 50 55 60  
 Gly Lys Phe Gln Gly Asn Asp Ala Phe Met Pro Phe Ala Ser Gly Ala  
 65 70 75 80  
 Gly Arg Gly Gly Arg Gly Pro Ala Trp Thr Gly Ser Gly Val Pro Gly  
 85 90 95  
 Ala His Cys Ala Pro Val Tyr Pro Ala Lys Gln Met Cys Leu Gly Thr  
 100 105 110  
 Gly Leu Ala His Ser Gly Ile Phe Leu Phe Leu Thr Ala Thr Leu Gln  
 115 120 125  
 Arg Phe Cys Leu Leu Pro Val Val Arg Pro Gly Thr Ile Asn Leu Thr  
 130 135 140  
 Cys Ser Ala Leu Ala Trp Ala Val Ser Pro Gln Thr Ser Ser Ser Ser  
 145 150 155 160  
 Gln Trp Pro Ala Glu Val Arg Leu His Tyr Gly Gly Leu Thr Gly Pro  
 165 170 175  
 Gln Thr Ser Ile Pro Ser Xaa Val Asn Lys Gly Pro Lys Leu Gln Lys  
 180 185 190

Lys

&lt;210&gt; 543

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (154)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (167)

&lt;223&gt; xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 543

Ser	Thr	Val	Arg	Xaa	Pro	Gly	Arg	Pro	Thr	Arg	Pro	Met	Ala	Ala	Glu
1				5					10						15

Glu	Pro	Gln	Gln	Gln	Lys	Gln	Glu	Pro	Leu	Gly	Ser	Asp	Ser	Glu	Val
			20					25					30		

Leu	Thr	Val	Trp	Pro	Met	Met	Lys	Pro	Ser	Trp	Leu	Ser	Arg	Thr	Glu
		35					40						45		

Phe	Ser	Lys	Arg	Leu	Leu	Cys	Arg	Thr	Leu	Trp	Cys	Gln	Ser	Gly	Trp
	50					55					60				

Ser	Ser	Arg	Ser	Tyr	Thr	Arg	Ser	Met	Leu	Lys	Met	Thr	Thr	Ser	Ile
65					70					75					80

Asn	Arg	Arg	Ser	Arg	Thr	Ser	Thr	Lys	Ser	Thr	Arg	Thr	Ser	Ala	Arg
				85					90					95	

Pro	Gly	Leu	Thr	Ala	Thr	Val	Ser	Ile	Gly	Leu	Ser	Asp	Ser	Pro	Thr
		100						105					110		

Trp	Arg	His	Cys	Trp	Met	Thr	Ala	Arg	Ser	Cys	Ser	Gly	Glu	Lys	Gly
	115						120					125			

Gly	His	Trp	Ala	Pro	Arg	Gln	Val	Gly	Val	Tyr	Leu	Leu	Pro	Gly	Arg
	130					135					140				

Val	Gly	Cys	Val	Ser	Ser	Arg	Val	Ser	Xaa	Ser	Phe	Pro	Gly	Asp	Gly
145					150					155					160

Leu	Asp	Ser	Gly	Leu	Ala	Xaa	Arg	Gly	Ser	Ala	Val	Ser	Ala	Leu	Ala
				165					170					175	

Ser	Gly	Leu	Val	Glu	Glu	Pro	Met	Leu	Gly	Pro	Pro	Phe	His	Pro	Thr
		180						185					190		

Pro	Arg	Phe	Lys	Ala	Val	Ser	Ala	Lys	Ser	Lys	Glu	Asp	Leu	Val	Ser
	195						200					205			

Gln Gly Phe Thr Glu Phe Thr Ile Glu Asp Phe His Asn Thr Phe Met  
 210 215 220  
 Asp Leu Ile Glu Gln Val Glu Lys Gln Thr Ser Val Ala Asp Leu Leu  
 225 230 235 240  
 Ala Ser Phe Asn Asp Gln Ser Thr Ser Asp Tyr Leu Val Val Tyr Leu  
 245 250 255  
 Arg Leu Leu Thr Ser Gly Tyr Leu Gln Arg Glu Ser Lys Phe Phe Glu  
 260 265 270  
 His Phe Ile Glu Gly Gly Arg Thr Val Lys Glu Phe Cys Gln Gln Glu  
 275 280 285  
 Val Glu Pro Met Cys Lys Glu Ser Asp His Ile His Ile Ile Ala Leu  
 290 295 300  
 Ala Gln Ala Leu Ser Val Ser Ile Gln Val Glu Tyr Met Asp Arg Gly  
 305 310 315 320  
 Glu Gly Gly Thr Thr Asn Pro His Ile Phe Pro Glu Gly Ser Glu Pro  
 325 330 335  
 Lys Val Tyr Leu Leu Tyr Arg Pro Gly His Tyr Asp Ile Leu Tyr Lys  
 340 345 350

&lt;210&gt; 544

&lt;211&gt; 240

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 544

Ser Thr His Ala Ser Glu Met Ala Glu Arg Gly Tyr Ser Phe Ser Leu  
 1 5 10 15  
 Thr Thr Phe Ser Pro Ser Gly Lys Leu Val Gln Ile Glu Tyr Ala Leu  
 20 25 30  
 Ala Ala Val Ala Gly Gly Ala Pro Ser Val Gly Ile Lys Ala Ala Asn  
 35 40 45  
 Gly Val Val Leu Ala Thr Glu Lys Lys Gln Lys Ser Ile Leu Tyr Asp  
 50 55 60  
 Glu Arg Ser Val His Lys Val Glu Pro Ile Thr Lys His Ile Gly Leu

498

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65              70              75              80
Val Tyr Ser Gly Met Gly Pro Asp Tyr Arg Val Leu Val His Arg Ala
              85              90              95
Arg Lys Leu Ala Gln Gln Tyr Tyr Leu Val Tyr Gln Glu Pro Ile Pro
              100              105              110
Thr Ala Gln Leu Val Gln Arg Val Ala Ser Val Met Gln Glu Tyr Thr
              115              120              125
Gln Ser Gly Gly Val Arg Pro Phe Gly Val Ser Leu Leu Ile Cys Gly
              130              135              140
Trp Asn Glu Gly Arg Pro Tyr Leu Phe Gln Ser Asp Pro Ser Gly Ala
              145              150              155              160
Tyr Phe Ala Trp Lys Ala Thr Ala Met Gly Lys Asn Tyr Val Asn Gly
              165              170              175
Lys Thr Phe Leu Glu Lys Arg Tyr Asn Glu Asp Leu Glu Leu Glu Asp
              180              185              190
Ala Ile His Thr Ala Ile Leu Thr Leu Lys Glu Ser Phe Glu Gly Gln
              195              200              205
Met Thr Glu Asp Asn Ile Glu Val Gly Ile Cys Asn Glu Ala Gly Phe
              210              215              220
Arg Arg Leu Thr Pro Thr Glu Val Lys Asp Tyr Leu Ala Ala Ile Ala
              225              230              235              240

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&lt;210&gt; 545

&lt;211&gt; 181

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 545

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Arg Cys Ile Leu Tyr Thr Gly Phe Met Leu Gly Ala Gln Arg Glu Val
  1              5              10              15
Asp Ser Arg Leu Leu Ala Leu Pro Gly Arg Lys Val Pro Thr Ser Trp
              20              25              30
Trp Asp Asp Leu Phe Lys Gly Ala Lys Glu His Gly Ala Val Ala Val
              35              40              45

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Glu Arg Val Thr Lys Ser Pro Gly Glu Thr Ser Lys Pro Arg Pro Phe  
 50 55 60  
 Ala Gly Gly Gly Tyr Arg Leu Gly Ala Ala Pro Glu Glu Glu Ser Ala  
 65 70 75 80  
 Tyr Val Ala Gly Glu Lys Arg Gln His Ser Ser Gln Asp Val His Val  
 85 90 95  
 Val Leu Lys Leu Trp Lys Ser Gly Phe Ser Leu Asp Asn Gly Glu Leu  
 100 105 110  
 Arg Ser Tyr Gln Asp Pro Ser Asn Ala Gln Phe Leu Glu Ser Ile Arg  
 115 120 125  
 Arg Gly Glu Val Pro Ala Glu Leu Arg Arg Leu Ala His Gly Gly Gln  
 130 135 140  
 Val Asn Leu Asp Met Glu Asp His Arg Asp Glu Asp Phe Val Lys Pro  
 145 150 155 160  
 Lys Gly Ala Phe Lys Ala Phe Thr Gly Glu Gly Gln Lys Leu Gly Ser  
 165 170 175  
 Thr Ala Pro Arg Cys  
 180

<210> 546  
 <211> 197  
 <212> PRT  
 <213> Homo sapiens

<400> 546  
 Pro Arg Val Arg Arg Arg Ala Arg Ala Ala Gly Ser Ser His Ala  
 1 5 10 15  
 Ala Met Ala Asp Ser Glu Leu Gln Leu Val Glu Gln Arg Ile Arg Ser  
 20 25 30  
 Phe Pro Asp Phe Pro Thr Pro Gly Val Val Phe Arg Asp Ile Ser Pro  
 35 40 45  
 Val Leu Lys Asp Pro Ala Ser Phe Arg Ala Ala Ile Gly Leu Leu Ala  
 50 55 60  
 Arg His Leu Lys Ala Thr His Gly Gly Arg Ile Asp Tyr Ile Ala Gly  
 65 70 75 80

500

Leu Asp Ser Arg Gly Phe Leu Phe Gly Pro Ser Leu Ala Gln Glu Leu  
                     85                    90                    95  
 Gly Leu Gly Cys Val Leu Ile Arg Lys Arg Gly Lys Leu Pro Gly Pro  
                     100                    105                    110  
 Thr Leu Trp Ala Ser Tyr Ser Leu Glu Tyr Gly Lys Ala Glu Leu Glu  
                     115                    120                    125  
 Ile Gln Lys Asp Ala Leu Glu Pro Gly Gln Arg Val Val Val Val Asp  
                     130                    135                    140  
 Asp Leu Leu Ala Thr Gly Gly Thr Met Asn Ala Ala Cys Glu Leu Leu  
                     145                    150                    155                    160  
 Gly Arg Leu Gln Ala Glu Val Leu Glu Cys Val Ser Leu Val Glu Leu  
                     165                    170                    175  
 Thr Ser Leu Lys Gly Arg Glu Lys Leu Ala Pro Val Pro Phe Phe Ser  
                     180                    185                    190  
 Leu Leu Gln Tyr Glu  
                     195

&lt;210&gt; 547

&lt;211&gt; 93

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (84)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 547

Glu Thr Gly Lys Glu Ser Lys Ala Leu Phe Leu Pro Phe Pro Gly Ser  
   1                    5                    10                    15  
 Val Tyr Ser Thr Ser Thr Gly Glu Ala Ser Gly Glu Gly Leu Ser Pro  
                     20                    25                    30  
 Leu Pro His Leu His Glu Phe Trp Asn Ser Val Leu Leu Ala Ala Cys  
                     35                    40                    45  
 Phe Gln Leu Pro Pro Ile Ser Ile Ala Ala Gly Ser Ser Cys Leu Phe  
                     50                    55                    60  
 Tyr Ser Val Ile Lys His Pro Ala Pro Thr Leu Ser Gln Arg Ser Ile  
   65                    70                    75                    80

Leu Ile Leu Xaa Lys Lys Ile Tyr Glu Glu Lys Lys Lys  
                     85                    90

<210> 548

<211> 49

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 548

Gly Leu Gln Leu Xaa Ala His Ala Ala Gly Arg Val Pro Gly Cys Ala  
     1                    5                    10                    15

Leu Gln Gly Leu Gly His Phe Leu Gln Glu Asn Lys Gln Leu Leu Arg  
                     20                    25                    30

Asp Val Leu Ala Gln Glu Leu His Lys Pro Ala Phe Glu Gly Arg His  
                     35                    40                    45

Ile

<210> 549

<211> 379

<212> PRT

<213> Homo sapiens

<400> 549

Val Ala Cys Cys Val Arg Ile Pro Gly Pro Pro Arg Arg Ser Gly Pro  
     1                    5                    10                    15

Ala Met Ala Val Thr Ile Thr Leu Lys Thr Leu Gln Gln Gln Thr Phe  
                     20                    25                    30

Lys Ile Arg Met Glu Pro Asp Glu Thr Val Lys Val Leu Lys Glu Lys  
                     35                    40                    45

Ile Glu Ala Glu Lys Gly Arg Asp Ala Phe Pro Val Ala Gly Gln Lys  
                     50                    55                    60

Leu Ile Tyr Ala Gly Lys Ile Leu Ser Asp Asp Val Pro Ile Arg Asp  
     65                    70                    75                    80

Tyr Arg Ile Asp Glu Lys Asn Phe Val Val Val Met Val Thr Lys Thr  
 85 90 95  
 Lys Ala Gly Gln Gly Thr Ser Ala Pro Pro Glu Ala Ser Pro Thr Ala  
 100 105 110  
 Ala Pro Glu Ser Ser Thr Ser Phe Pro Pro Ala Pro Thr Ser Gly Met  
 115 120 125  
 Ser His Pro Pro Pro Ala Ala Arg Glu Asp Lys Ser Pro Ser Glu Glu  
 130 135 140  
 Ser Ala Pro Thr Thr Ser Pro Glu Ser Val Ser Gly Ser Val Pro Ser  
 145 150 155 160  
 Ser Gly Ser Ser Gly Arg Glu Glu Asp Ala Ala Ser Thr Leu Val Thr  
 165 170 175  
 Gly Ser Glu Tyr Glu Thr Met Leu Thr Glu Ile Met Ser Met Gly Tyr  
 180 185 190  
 Glu Arg Glu Arg Val Val Ala Ala Leu Arg Ala Ser Tyr Asn Asn Pro  
 195 200 205  
 His Arg Ala Val Glu Tyr Leu Leu Thr Gly Ile Pro Gly Ser Pro Glu  
 210 215 220  
 Pro Glu His Gly Ser Val Gln Glu Ser Gln Val Ser Glu Gln Pro Ala  
 225 230 235 240  
 Thr Glu Ala Gly Glu Asn Pro Leu Glu Phe Leu Arg Asp Gln Pro Gln  
 245 250 255  
 Phe Gln Asn Met Arg Gln Val Ile Gln Gln Asn Pro Ala Leu Leu Pro  
 260 265 270  
 Ala Leu Leu Gln Gln Leu Gly Gln Glu Asn Pro Gln Leu Leu Gln Gln  
 275 280 285  
 Ile Ser Arg His Gln Glu Gln Phe Ile Gln Met Leu Asn Glu Pro Pro  
 290 295 300  
 Gly Glu Leu Ala Asp Ile Ser Asp Val Glu Gly Glu Val Gly Ala Ile  
 305 310 315 320  
 Gly Glu Glu Ala Pro Gln Met Asn Tyr Ile Gln Val Thr Pro Gln Glu  
 325 330 335  
 Lys Glu Ala Ile Glu Arg Leu Lys Ala Leu Gly Phe Pro Glu Ser Leu  
 340 345 350

Val Ile Gln Ala Tyr Phe Ala Cys Glu Lys Asn Glu Asn Leu Ala Ala  
355 360 365

Asn Phe Leu Leu Ser Gln Asn Phe Asp Asp Glu  
370 375

<210> 550

<211> 275

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (260)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (261)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (267)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (272)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 550

Cys Ser Cys Lys Arg Xaa His Gln Gln Gln Val Leu Pro Pro Arg Gln  
1 5 10 15

Pro Ser Ala Leu Val Pro Ser Val Thr Glu Tyr Arg Leu Asp Gly His  
20 25 30

Thr Ile Ser Asp Leu Ser Arg Ser Ser Arg Gly Glu Leu Ile Pro Ile  
           35                          40                          45  
 Ser Pro Ser Thr Glu Val Gly Gly Ser Gly Ile Gly Thr Pro Pro Ser  
           50                          55                          60  
 Val Leu Lys Arg Gln Arg Lys Arg Arg Val Ala Leu Ser Pro Val Thr  
           65                          70                          75                          80  
 Glu Asn Ser Thr Ser Leu Ser Phe Leu Asp Ser Cys Asn Ser Leu Thr  
                           85                          90                          95  
 Pro Lys Ser Thr Pro Val Lys Thr Leu Pro Phe Ser Pro Ser Gln Phe  
                           100                          105                          110  
 Leu Asn Phe Trp Asn Lys Gln Asp Thr Leu Glu Leu Glu Ser Pro Ser  
           115                          120                          125  
 Leu Thr Ser Thr Pro Val Cys Ser Gln Lys Val Val Val Thr Thr Pro  
           130                          135                          140  
 Leu His Arg Asp Lys Thr Pro Leu His Gln Lys His Ala Ala Phe Val  
           145                          150                          155                          160  
 Thr Pro Asp Gln Lys Tyr Ser Met Asp Asn Thr Pro His Thr Pro Thr  
                           165                          170                          175  
 Pro Phe Lys Asn Ala Leu Glu Lys Tyr Gly Pro Leu Lys Pro Leu Pro  
           180                          185                          190  
 Gln Thr Pro His Leu Glu Glu Asp Leu Lys Glu Val Leu Arg Ser Glu  
           195                          200                          205  
 Ala Gly Ile Glu Leu Ile Ile Glu Asp Asp Ile Arg Pro Glu Lys Gln  
           210                          215                          220  
 Lys Arg Lys Pro Gly Leu Arg Arg Ser Pro Xaa Lys Lys Val Arg Lys  
           225                          230                          235                          240  
 Ser Leu Ala Leu Asp Ile Val Asp Glu Asp Val Lys Leu Met Met Ser  
           245                          250                          255  
 Thr Leu Pro Xaa Xaa Leu Ser Leu Ala Thr Xaa Ala Pro Cys Lys Xaa  
           260                          265                          270  
 Phe Gln Pro  
           275

&lt;211&gt; 161

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (158)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 551

Asn Leu Ala Ala Ala Ser Gly Gly Gly Pro Gln Ser Val Ser Gly Thr  
1 5 10 15

Leu Leu Cys Glu Pro Val Leu Thr Met Phe Ala Thr Ser Gly Ala Val  
20 25 30

Ala Ala Gly Lys Pro Tyr Ser Cys Ser Glu Cys Gly Lys Ser Phe Cys  
35 40 45

Tyr Ser Ser Val Leu Leu Arg His Glu Arg Ala His Gly Gly Asp Gly  
50 55 60

Arg Phe Arg Cys Leu Glu Cys Gly Glu Arg Cys Ala Arg Ala Ala Asp  
65 70 75 80

Leu Arg Ala His Arg Arg Thr His Ala Gly Gln Thr Leu Tyr Ile Cys  
85 90 95

Ser Glu Cys Gly Gln Ser Phe Arg His Ser Gly Arg Leu Asp Leu His  
100 105 110

Leu Gly Ala His Arg Gln Arg Cys Arg Thr Cys Pro Cys Arg Thr Cys  
115 120 125

Gly Arg Arg Phe Pro His Leu Pro Ala Leu Leu Leu His Arg Arg Arg  
130 135 140

Gln His Leu Pro Glu Arg Pro Arg Arg Cys Pro Leu Cys Xaa Leu Arg  
145 150 155 160

Phe

&lt;210&gt; 552

&lt;211&gt; 405

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 552

506

Pro Arg Val Arg Arg Arg Ala Arg Gly Arg Arg Val Arg Pro Ala Gly  
 1 5 10 15  
 Gly Pro Val Arg Arg Gly Ala Ala Val Arg Gly Ala Leu Arg Gly Ala  
 20 25 30  
 Ser Leu Gly His Gly Ala Ala Ala Arg Ala Gly Arg Pro Leu Cys Val  
 35 40 45  
 Arg His Ser Glu Pro Val Cys Gly Ser Asp Ala Asn Thr Tyr Ala Asn  
 50 55 60  
 Leu Cys Gln Leu Arg Ala Ala Ser Arg Arg Ser Glu Arg Leu His Arg  
 65 70 75 80  
 Pro Pro Val Ile Val Leu Gln Arg Gly Ala Cys Gly Gln Gly Gln Glu  
 85 90 95  
 Asp Pro Asn Ser Leu Arg His Lys Tyr Asn Phe Ile Ala Asp Val Val  
 100 105 110  
 Glu Lys Ile Ala Pro Ala Val Val His Ile Glu Leu Phe Arg Lys Leu  
 115 120 125  
 Pro Phe Ser Lys Arg Glu Val Pro Val Ala Ser Gly Ser Gly Phe Ile  
 130 135 140  
 Val Ser Glu Asp Gly Leu Ile Val Thr Asn Ala His Val Val Thr Asn  
 145 150 155 160  
 Lys His Arg Val Lys Val Glu Leu Lys Asn Gly Ala Thr Tyr Glu Ala  
 165 170 175  
 Lys Ile Lys Asp Val Asp Glu Lys Ala Asp Ile Ala Leu Ile Lys Ile  
 180 185 190  
 Asp His Gln Gly Lys Leu Pro Val Leu Leu Leu Gly Arg Ser Ser Glu  
 195 200 205  
 Leu Arg Pro Gly Glu Phe Val Val Ala Ile Gly Ser Pro Phe Ser Leu  
 210 215 220  
 Gln Asn Thr Val Thr Thr Gly Ile Val Ser Thr Thr Gln Arg Gly Gly  
 225 230 235 240  
 Lys Glu Leu Gly Leu Arg Asn Ser Asp Met Asp Tyr Ile Gln Thr Asp  
 245 250 255  
 Ala Ile Ile Asn Tyr Gly Asn Ser Gly Gly Pro Leu Val Asn Leu Asp  
 260 265 270



Gly Glu Val Ile Gly Ile Asn Thr Leu Lys Val Thr Ala Gly Ile Ser  
 275 280 285  
 Phe Ala Ile Pro Ser Asp Lys Ile Lys Lys Phe Leu Thr Glu Ser His  
 290 295 300  
 Asp Arg Gln Ala Lys Gly Lys Ala Ile Thr Lys Lys Lys Tyr Ile Gly  
 305 310 315 320  
 Ile Arg Met Met Ser Leu Thr Ser Ser Lys Ala Lys Glu Leu Lys Asp  
 325 330 335  
 Arg His Arg Asp Phe Pro Asp Val Ile Ser Gly Ala Tyr Ile Ile Glu  
 340 345 350  
 Val Ile Pro Asp Thr Pro Ala Glu Ala Gly Gly Leu Lys Glu Asn Asp  
 355 360 365  
 Val Ile Ile Ser Ile Asn Gly Gln Ser Val Val Ser Ala Asn Asp Val  
 370 375 380  
 Ser Asp Val Ile Lys Arg Glu Ser Thr Leu Asn Met Val Val Arg Arg  
 385 390 395 400  
 Val Met Lys Ile Ser  
 405

<210> 553  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 553  
 Ala Gln Glu Asn Glu Glu Met Glu Gln Pro Met Gln Asn Gly Glu Glu  
 1 5 10 15  
 Asp Arg Pro Leu Gly Gly Gly Glu Gly His Gln Pro Ala Gly Asn Arg  
 20 25 30  
 Arg Gly Gln Ala Arg Arg Leu Ala Pro Asn Phe Arg Trp Ala Ile Pro  
 35 40 45  
 Asn Arg Gln Ile Asn Asp Gly Met Gly Gly Asp Gly Asp Asp Met Glu  
 50 55 60  
 Ile Phe Met Glu Glu Met Arg Glu Ile Arg Arg Lys Leu Arg Glu Leu  
 65 70 75 80  
 Gln Leu Arg Asn Cys Leu Arg Ile Leu Met Gly Glu Leu Ser Asn His

85 90 95

His Asp His His Asp Glu Phe Cys Leu Met Pro  
100 105

<210> 554  
<211> 229  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (8)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (15)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (20)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (27)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (78)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 554  
Gly Leu Ser Ala Glu Ser Thr Xaa Thr Ser Thr Met Pro Met Xaa Leu  
1 5 10 15  
Gly Tyr Trp Xaa Ile Arg Gly Leu Ala His Xaa Ile Arg Leu Leu Leu  
20 25 30  
Glu Tyr Thr Asp Ser Ser Tyr Glu Glu Lys Lys Tyr Thr Met Gly Asp  
35 40 45  
Ala Pro Asp Tyr Asp Arg Ser Gln Trp Leu Asn Glu Lys Phe Lys Leu  
50 55 60  
Gly Leu Asp Phe Pro Asn Leu Pro Tyr Leu Ile Asp Gly Xaa His Lys

**<221> SITE**

&lt;222&gt; (72)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (98)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 555

Asn	Val	Ile	Ser	Val	Asp	Pro	Asn	Asp	Gln	Lys	Lys	Thr	Ala	Cys	Tyr
1				5					10					15	

Asp	Ile	Asp	Val	Glu	Val	Asp	Asp	Thr	Leu	Lys	Thr	Gln	Met	Asn	Ser
			20					25					30		

Phe	Leu	Leu	Ser	Thr	Ala	Ser	Gln	Gln	Glu	Ile	Ala	Thr	Leu	Asp	Asn
	35						40					45			

Lys	Thr	Met	Thr	Asp	Val	Val	Gly	Asn	Gln	Xaa	Xaa	Ser	Ala	Glu	Leu
	50					55					60				

Ser	Ser	Thr	Ser	Ser	Pro	Gly	Xaa	Gly	Gly	Cys	Val	Pro	Ile	Leu	Leu
65					70					75				80	

Leu	Gln	Gly	Ala	Ala	Glu	Thr	Thr	Arg	Ile	Arg	Ala	Ser	Pro	Gly	Asn
			85					90						95	

Pro	Xaa	Tyr	Ile	Gly	Pro	Leu	Pro	Gln	Pro
		100					105		

&lt;210&gt; 556

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 556

Gly	Arg	Ala	Thr	Lys	Gln	Asn	Thr	Thr	Lys	Pro	Asn	His	Arg	Ile	Ile
1				5					10					15	

Phe	Asn	Pro	Thr	Phe	Tyr	Thr	Met	Pro	Gln	Phe	Pro	Ile	Thr	Leu	His
			20					25					30		

Thr	Ser	Phe	Cys	Val	Gln	Leu	Asn	Cys	Asn	Cys	Phe	Leu	Tyr	Leu	Glu
	35					40						45			

Arg	Val	Thr	Ile	Glu	Leu	Glu	Thr	Phe	Tyr	Ser	Gly	Arg	Leu	Gly	Ser
	50					55					60				

Phe	Trp	Trp	Asp	Ser	Val	Gly	Glu	Arg	Glu	Glu	Gly	Glu	Val	Gly	Gly
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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<210> 557
<211> 565
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (57)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (71)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (75)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (82)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>  
<221> SITE  
<222> (118)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>  
<221> SITE  
<222> (120)  
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (552)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 557  
Ala Ser Leu Thr Gly Thr Gln Ala Leu Pro Pro Leu Phe Ser Leu Gly  
1 5 10 15

Tyr His Gln Ser Arg Trp Asn Tyr Arg Asp Glu Ala Asp Val Leu Glu  
 20 25 30  
 Val Asp Gln Gly Phe Asp Asp His Asn Leu Pro Cys Asp Val Ile Trp  
 35 40 45  
 Leu Asp Ile Glu His Ala Asp Gly Xaa Arg Tyr Phe Thr Trp Asp Pro  
 50 55 60  
 Ser Arg Phe Pro Gln Pro Xaa Thr Met Leu Xaa Arg Leu Ala Ser Lys  
 65 70 75 80  
 Arg Xaa Lys Leu Val Ala Ile Val Asp Pro His Ile Lys Val Asp Ser  
 85 90 95  
 Gly Tyr Arg Val His Glu Glu Leu Arg Asn Leu Gly Leu Tyr Val Lys  
 100 105 110  
 Thr Arg Asp Gly Ser Xaa Tyr Xaa Gly Trp Cys Trp Pro Gly Ser Ala  
 115 120 125  
 Gly Tyr Pro Asp Phe Thr Asn Pro Thr Met Arg Ala Trp Trp Ala Asn  
 130 135 140  
 Met Phe Ser Tyr Asp Asn Tyr Glu Gly Ser Ala Pro Asn Leu Phe Val  
 145 150 155 160  
 Trp Asn Asp Met Asn Glu Pro Ser Val Phe Asn Gly Pro Glu Val Thr  
 165 170 175  
 Met Leu Lys Asp Ala Gln His Tyr Gly Gly Trp Glu His Arg Asp Val  
 180 185 190  
 His Asn Ile Tyr Gly Leu Tyr Val His Met Ala Thr Ala Asp Gly Leu  
 195 200 205  
 Arg Gln Arg Ser Gly Gly Met Glu Arg Pro Phe Val Leu Ala Arg Ala  
 210 215 220  
 Phe Phe Ala Gly Ser Gln Arg Phe Gly Ala Val Trp Thr Gly Asp Asn  
 225 230 235 240  
 Thr Ala Glu Trp Asp His Leu Lys Ile Ser Ile Pro Met Cys Leu Ser  
 245 250 255  
 Leu Gly Leu Val Gly Leu Ser Phe Cys Gly Ala Asp Val Gly Gly Phe  
 260 265 270  
 Phe Lys Asn Pro Glu Pro Glu Leu Leu Val Arg Trp Tyr Gln Met Gly  
 275 280 285

Ala Tyr Gln Pro Phe Phe Arg Ala His Ala His Leu Asp Thr Gly Arg  
 290 295 300  
 Arg Glu Pro Trp Leu Leu Pro Ser Gln His Asn Asp Ile Ile Arg Asp  
 305 310 315 320  
 Ala Leu Gly Gln Arg Tyr Ser Leu Leu Pro Phe Trp Tyr Thr Leu Leu  
 325 330 335  
 Tyr Gln Ala His Arg Glu Gly Ile Pro Val Met Arg Pro Leu Trp Val  
 340 345 350  
 Gln Tyr Pro Gln Asp Val Thr Thr Phe Asn Ile Asp Asp Gln Tyr Leu  
 355 360 365  
 Leu Gly Asp Ala Leu Leu Val His Pro Val Ser Asp Ser Gly Ala His  
 370 375 380  
 Gly Val Gln Val Tyr Leu Pro Gly Gln Gly Glu Val Trp Tyr Asp Ile  
 385 390 395 400  
 Gln Ser Tyr Gln Lys His His Gly Pro Gln Thr Leu Tyr Leu Pro Val  
 405 410 415  
 Thr Leu Ser Ser Ile Pro Val Phe Gln Arg Gly Gly Thr Ile Val Pro  
 420 425 430  
 Arg Trp Met Arg Val Arg Arg Ser Ser Glu Cys Met Lys Asp Asp Pro  
 435 440 445  
 Ile Thr Leu Phe Val Ala Leu Ser Pro Gln Gly Thr Ala Gln Gly Glu  
 450 455 460  
 Leu Phe Leu Asp Asp Gly His Thr Phe Asn Tyr Gln Thr Arg Gln Glu  
 465 470 475 480  
 Phe Leu Leu Arg Arg Phe Ser Phe Ser Gly Asn Thr Leu Val Ser Ser  
 485 490 495  
 Ser Ala Asp Pro Glu Gly His Phe Glu Thr Pro Ile Trp Ile Glu Arg  
 500 505 510  
 Val Val Ile Ile Gly Ala Gly Lys Pro Ala Ala Val Val Leu Gln Thr  
 515 520 525  
 Lys Gly Ser Pro Glu Ser Arg Leu Ser Phe Gln His Asp Pro Glu Thr  
 530 535 540  
 Ser Val Leu Val Leu Arg Lys Xaa Gly Ile Asn Val Ala Ser Asp Trp  
 545 550 555 560

Ser Ile His Leu Arg  
565

<210> 558

<211> 160

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 558

Arg	Glu	Ala	Val	Leu	Pro	Gln	Ala	Val	Leu	Arg	His	Pro	Val	Arg	Thr
1				5					10					15	
Gln	Arg	Arg	Glu	His	Arg	Gly	Arg	Gly	Leu	Leu	His	Leu	Arg	Glu	Ala
			20					25						30	
Pro	Gly	Gly	Gly	Ala	Ala	Xaa	His	Arg	Pro	His	Arg	Gly	Pro	Arg	Gly
			35					40						45	
Pro	Ser	Arg	Gly	Ala	Glu	Gly	Glu	Arg	Pro	Pro	Glu	Gly	Pro	Ser	Arg
			50				55					60			
Ala	Ser	Ser	Val	Thr	Thr	Phe	Thr	Gly	Glu	Pro	Asn	Thr	Cys	Pro	Arg
			65				70				75				80
Cys	Ser	Lys	Lys	Val	Tyr	Phe	Ala	Glu	Lys	Val	Thr	Ser	Leu	Gly	Lys
				85						90					95
Asp	Trp	His	Arg	Pro	Cys	Leu	Arg	Cys	Glu	Arg	Cys	Gly	Lys	Thr	Leu
				100					105					110	
Thr	Pro	Gly	Gly	His	Ala	Glu	His	Asp	Gly	Gln	Pro	Tyr	Cys	His	Lys
				115				120						125	
Pro	Cys	Tyr	Gly	Ile	Leu	Phe	Gly	Pro	Lys	Gly	Val	Asn	Thr	Gly	Ala
				130			135					140			
Val	Gly	Ser	Tyr	Ile	Tyr	Asp	Arg	Asp	Pro	Glu	Gly	Lys	Val	Gln	Pro
				145			150				155				160



&lt;210&gt; 559

&lt;211&gt; 480

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 559

Gly Cys Ile Gly Tyr Leu Val Leu Leu Trp Pro Leu Pro Leu Ile His  
 1 5 10 15  
 Phe Gly Leu Ala Asn Gln Ser Glu Asp Leu Ser Val Phe Tyr Pro Gly  
 20 25 30  
 Thr Leu Leu Glu Thr Gly His Asp Ile Leu Phe Phe Trp Val Ala Arg  
 35 40 45  
 Met Val Met Leu Gly Leu Lys Leu Thr Gly Arg Leu Pro Phe Arg Glu  
 50 55 60  
 Val Tyr Leu His Ala Ile Val Arg Asp Ala His Gly Arg Lys Met Ser  
 65 70 75 80  
 Lys Ser Leu Gly Asn Val Ile Asp Pro Leu Asp Val Ile Tyr Gly Ile  
 85 90 95  
 Ser Leu Gln Gly Leu His Asn Gln Leu Leu Asn Ser Asn Leu Asp Pro  
 100 105 110  
 Ser Glu Val Glu Lys Ala Lys Glu Gly Gln Lys Ala Asp Phe Pro Ala  
 115 120 125  
 Gly Ile Pro Glu Cys Gly Thr Asp Ala Leu Arg Phe Gly Leu Cys Ala  
 130 135 140  
 Tyr Met Ser Gln Gly Arg Asp Ile Asn Leu Asp Val Asn Arg Ile Leu  
 145 150 155 160  
 Gly Tyr Arg His Phe Cys Asn Lys Leu Trp Asn Ala Thr Lys Phe Ala  
 165 170 175  
 Leu Arg Gly Leu Gly Lys Gly Phe Val Pro Ser Pro Thr Ser Gln Pro  
 180 185 190  
 Gly Gly His Glu Ser Leu Val Asp Arg Trp Ile Arg Ser Arg Leu Thr  
 195 200 205  
 Glu Ala Val Arg Leu Ser Asn Gln Gly Phe Gln Ala Tyr Asp Phe Pro  
 210 215 220  
 Ala Val Thr Thr Ala Gln Tyr Ser Phe Trp Leu Tyr Glu Leu Cys Asp  
 225 230 235 240

516

Val Tyr Leu Glu Cys Leu Lys Pro Val Leu Asn Gly Val Asp Gln Val  
245 250 255

Ala Ala Glu Cys Ala Arg Gln Thr Leu Tyr Thr Cys Leu Asp Val Gly  
260 265 270

Leu Arg Leu Leu Ser Pro Phe Met Pro Phe Val Thr Glu Glu Leu Phe  
275 280 285

Gln Arg Leu Pro Arg Arg Met Pro Gln Ala Pro Pro Ser Leu Cys Val  
290 295 300

Thr Pro Tyr Pro Glu Pro Ser Glu Cys Ser Trp Lys Asp Pro Glu Ala  
305 310 315 320

Glu Ala Ala Leu Glu Leu Ala Leu Ser Ile Thr Arg Ala Val Arg Ser  
325 330 335

Leu Arg Ala Asp Tyr Asn Leu Thr Arg Ile Arg Pro Asp Cys Phe Leu  
340 345 350

Glu Val Ala Asp Glu Ala Thr Gly Ala Leu Ala Ser Ala Val Ser Gly  
355 360 365

Tyr Val Gln Ala Leu Ala Ser Ala Gly Val Val Ala Val Leu Ala Leu  
370 375 380

Gly Ala Pro Ala Pro Gln Gly Cys Ala Val Ala Leu Ala Ser Asp Arg  
385 390 395 400

Cys Ser Ile His Leu Gln Leu Gln Gly Leu Val Asp Pro Ala Arg Glu  
405 410 415

Leu Gly Lys Leu Gln Ala Lys Arg Val Glu Ala Gln Arg Gln Ala Gln  
420 425 430

Arg Leu Arg Glu Arg Arg Ala Ala Ser Gly Tyr Pro Val Lys Val Pro  
435 440 445

Leu Glu Val Gln Glu Ala Asp Glu Ala Lys Leu Gln Gln Thr Glu Ala  
450 455 460

Glu Leu Arg Lys Val Asp Glu Ala Ile Ala Leu Phe Gln Lys Met Leu  
465 470 475 480

&lt;210&gt; 560

&lt;211&gt; 96

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 560

Ala Cys Leu Glu Arg Cys Gly Ser Trp Arg Pro His Arg Pro Met Thr  
1 5 10 15

Ser Gly Ala Arg Glu Asn Pro Ile Gln Val Pro Arg Ser Ser Leu Glu  
20 25 30

Ala Thr Gly Ala Gln Glu Arg Trp Ala Glu Asp Val Pro Tyr Pro Thr  
35 40 45

Thr Arg Ala Val Ser Leu Pro Pro Ser Leu Gly Val Gly Ser Thr Gly  
50 55 60

Met Ser Ser Ser Arg Phe Leu Gly Ser Leu Gly Lys His Gly Arg Leu  
65 70 75 80

Asp Ser Ser Arg Arg Ala Arg Leu Trp Gly Arg Gly Gly Arg Gly Gly  
85 90 95

&lt;210&gt; 561

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 561

Ile Arg His Glu Ser Ser Ile Leu Ser Val Leu Phe Ile Arg Phe Leu  
1 5 10 15

Lys Cys Ala Asp Pro Phe Lys Thr Pro Ala Tyr Leu Cys Asn Lys Glu  
20 25 30

Lys Tyr Ser Lys Ile Leu Pro Ser Phe Ser His Thr Val Leu Lys Met  
35 40 45

Leu Gln Asp Gln Ile Ile Ala His Lys Ile Arg Ser  
50 55 60

&lt;210&gt; 562

&lt;211&gt; 241

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 562

Ser Ser Met Ala Lys Pro Cys Gly Val Arg Leu Ser Gly Glu Ala Arg  
 1 5 10 15  
 Lys Gln Val Glu Val Phe Arg Gln Asn Leu Phe Gln Glu Ala Glu Glu  
 20 25 30  
 Phe Leu Tyr Arg Phe Leu Pro Gln Lys Ile Ile Tyr Leu Asn Gln Leu  
 35 40 45  
 Leu Gln Glu Asp Ser Leu Asn Val Ala Asp Leu Thr Ser Leu Arg Ala  
 50 55 60  
 Pro Leu Asp Ile Pro Ile Pro Asp Pro Pro Pro Lys Asp Asp Glu Met  
 65 70 75 80  
 Glu Thr Asp Lys Gln Glu Lys Lys Glu Val Pro Lys Cys Gly Phe Leu  
 85 90 95  
 Pro Gly Asn Glu Lys Val Leu Ser Leu Leu Ala Leu Val Lys Pro Glu  
 100 105 110  
 Val Trp Thr Leu Lys Glu Lys Cys Ile Leu Val Ile Thr Trp Ile Gln  
 115 120 125  
 His Leu Ile Pro Lys Ile Glu Asp Gly Asn Asp Phe Gly Val Ala Ile  
 130 135 140  
 Gln Glu Lys Val Leu Glu Arg Val Asn Ala Val Lys Thr Lys Val Glu  
 145 150 155 160  
 Ala Phe Gln Thr Thr Ile Ser Lys Tyr Phe Ser Glu Arg Gly Asp Ala  
 165 170 175  
 Val Ala Lys Ala Ser Lys Glu Thr His Val Met Asp Tyr Arg Ala Leu  
 180 185 190  
 Val His Glu Arg Asp Glu Ala Ala Tyr Gly Glu Leu Arg Ala Met Val  
 195 200 205  
 Leu Asp Leu Arg Ala Phe Tyr Ala Glu Leu Tyr His Ile Ile Ser Ser  
 210 215 220  
 Asn Leu Glu Lys Ile Val Asn Pro Lys Gly Glu Glu Lys Pro Ser Met  
 225 230 235 240  
 Tyr

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<220>
<221> SITE
<222> (145)
<223> Xaa equals any of the naturally occurring L-amino acids
```

Leu Gly Ser Ile Gln Val Met Gln Ala Val Arg Asn Ala Gly Ser Arg  
1 5 10 15

Phe Leu Arg Ser Trp Thr Trp Pro Gln Thr Ala Gly Arg Val Val Ala  
20 25 30

Arg Thr Pro Ala Gly Thr Ile Cys Thr Gly Ala Arg Gln Leu Gln Asp  
35 40 45

Ala Ala Ala Lys Gln Lys Val Glu Gln Asn Ala Ala Pro Ser His Thr  
50 55 60

Lys Phe Ser Ile Tyr Pro Pro Ile Pro Gly Glu Glu Ser Ser Leu Arg  
65 70 75 80

Trp Ala Gly Lys Lys Phe Glu Glu Ile Pro Ile Ala His Ile Lys Ala  
85 90 95

Ser His Asn Asn Thr Gln Ile Gln Val Val Ser Ala Ser Asn Glu Pro  
100 105 110

Leu Ala Phe Ala Ser Cys Gly Thr Glu Gly Phe Arg Asn Ala Lys Lys  
115 120 125

Gly Thr Gly Ile Ala Ala Gln Thr Ala Gly Ile Ala Ala Ala Ala Arg  
130 135 140

Xaa Lys Gln Lys Gly Val Ile His Ile Arg Val Val Val Lys Gly Leu  
145                      150                      155                      160

Gly Pro Gly Arg Leu Ser Ala Met His Gly Leu Ile Met Gly Gly Leu  
165 170 175

Glu Val Ile Ser Ile Thr Asp Asn Thr Pro Ile Pro His Asn Gly Cys  
180 185 190

Arg Pro Arg Lys Ala Arg Lys Leu  
195 200

&lt;210&gt; 564

&lt;211&gt; 115

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 564

Val Arg Leu Val Pro Gly Ala Asp Lys Tyr Asn Asp Asp Ile Arg Lys  
1 5 10 15

Gly Ile Val Leu Leu Glu Glu Leu Leu Pro Lys Gly Ser Lys Glu Glu  
20 25 30

Gln Arg Asp Tyr Val Phe Tyr Leu Ala Val Gly Asn Tyr Arg Leu Lys  
35 40 45

Glu Tyr Glu Lys Ala Leu Lys Tyr Val Arg Gly Leu Leu Gln Thr Glu  
50 55 60

Pro Gln Asn Asn Gln Ala Lys Glu Leu Glu Arg Leu Ile Asp Lys Ala  
65 70 75 80

Met Lys Lys Asp Gly Leu Val Gly Met Ala Ile Val Gly Gly Met Ala  
85 90 95

Leu Gly Val Ala Gly Leu Ala Gly Leu Ile Gly Leu Ala Val Ser Lys  
100 105 110

Ser Lys Ser  
115

&lt;210&gt; 565

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 565

Pro Thr Arg Pro Asp Glu His Asp Glu Asn Asn Ala Glu Ala Ser Ala  
1 5 10 15

Glu Leu Ser Asn Glu Gly Val Met Asn His Arg Ser Glu Glu Glu Arg  
20 25 30

Val Thr Glu Thr Gln Lys Asn Glu Arg Val Lys Lys Gln Leu Gln Ala  
35 40 45

Leu Ser Ser Glu Leu Ala Gln Ala Arg Asp Glu Thr Lys Lys Thr Gln

50 55 60  
Asn Asp Val Leu His Ala Glu Asn Val Lys Ala Gly Arg Asp Lys Tyr  
65 70 75 80  
Lys Thr Leu Arg Gln Ile Arg Gln Gly Asn Thr Lys Gln Arg Ile Asp  
85 90 95  
Glu Phe Glu Ala Met  
100

<210> 566  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 566  
Thr Ala Asp Leu Val Ile Arg Pro Pro Arg Pro Leu Lys Val Leu Gly  
1 5 10 15

Phe Cys Val Phe Cys Ala Pro Pro Leu  
20 25

<210> 567  
<211> 274  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (182)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (216)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (222)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (224)  
<223> Xaa equals any of the naturally occurring L-amino acids

522

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (228)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (231)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 567

Ala	Ser	Pro	Glu	Val	Glu	Ala	Gly	Ala	Ala	Arg	Gln	Pro	Leu	Leu	Gly
1				5						10				15	

Val	Ala	Gly	Gly	Gln	Thr	Leu	Gly	Ala	Thr	Pro	Gly	Pro	Val	Met	Asn
		20					25						30		

Gly	Pro	Ala	Asp	Gly	Glu	Val	Asp	Tyr	Lys	Lys	Lys	Tyr	Arg	Asn	Leu
		35				40						45			

Lys	Arg	Lys	Leu	Lys	Phe	Leu	Ile	Tyr	Glu	His	Glu	Cys	Phe	Gln	Glu
	50					55					60				

Glu	Leu	Arg	Lys	Ala	Gln	Arg	Lys	Leu	Leu	Lys	Val	Ser	Arg	Asp	Lys
	65				70					75					80

Ser	Phe	Leu	Leu	Asp	Arg	Leu	Leu	Gln	Tyr	Glu	Asn	Val	Asp	Glu	Asp
			85					90						95	

Ser	Ser	Asp	Ser	Asp	Ala	Thr	Ala	Ser	Ser	Asp	Asn	Ser	Glu	Thr	Glu
		100						105					110		

Gly	Thr	Pro	Lys	Leu	Ser	Asp	Thr	Pro	Ala	Pro	Lys	Arg	Lys	Arg	Ser
	115						120					125			

Pro	Pro	Leu	Gly	Gly	Ala	Pro	Ser	Pro	Ser	Ser	Leu	Ser	Leu	Pro	Pro
	130					135					140				

Ser	Thr	Gly	Phe	Pro	Leu	Gln	Ala	Ser	Gly	Val	Pro	Ser	Pro	Tyr	Leu
	145				150					155					160

Ser	Ser	Leu	Ala	Ser	Ser	Arg	Tyr	Pro	Pro	Phe	Pro	Ser	Asp	Tyr	Leu
			165					170						175	

Ala	Leu	Gln	Leu	Pro	Xaa	Pro	Ser	Pro	Leu	Arg	Pro	Lys	Arg	Glu	Lys
		180						185					190		

Arg	Pro	Arg	Leu	Pro	Arg	Lys	Leu	Lys	Met	Ala	Val	Gly	Pro	Pro	Asp
		195					200					205			



Cys Pro Val Gly Gly Pro Leu Xaa Phe Pro Gly Arg Gly Xaa Gly Xaa  
 210 215 220

Gly Val Gly Xaa Thr Leu Xaa Pro Leu Pro Pro Pro Lys Met Pro Pro  
 225 230 235 240

Pro Thr Ile Leu Ser Thr Val Pro Arg Gln Met Phe Ser Asp Ala Gly  
 245 250 255

Ser Gly Asp Asp Ala Leu Asp Gly Asp Asp Asp Leu Val Ile Asp Ile  
 260 265 270

Pro Glu

<210> 568

<211> 133

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 568

Ala Arg Gly Asp His Val Arg Ser Arg Glu Thr Gly Arg Gln Ser Ala  
 1 5 10 15

Ser Lys Gly Gln Ile Pro Leu Leu Pro Arg Gly Pro Ala Val Pro Gly  
 20 25 30

Gly Pro Ser Ala Gln Thr Ala Ala Gln Arg Glu Leu Arg Gly Xaa Val  
 35 40 45

Gly Ala Gly Ala Pro Val Tyr Leu Ala Ala Val Leu Glu Tyr Leu Thr  
 50 55 60

Ala Glu Ile Leu Glu Leu Ala Gly Asn Ala Ala Arg Asp Asn Lys Lys  
 65 70 75 80

Thr Arg Ile Ile Pro Arg His Leu Gln Leu Ala Ile Arg Asn Asp Glu  
 85 90 95

Glu Leu Asn Lys Leu Leu Gly Lys Val Thr Ile Ala Gln Gly Gly Val  
 100 105 110

Leu Pro Asn Ile Gln Ala Val Leu Leu Pro Lys Lys Thr Glu Ser Gln  
 115 120 125

Lys Thr Lys Ser Lys  
130

<210> 569

<211> 153

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (136)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (137)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (152)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 569

Met Cys Arg Gly Tyr Ala Trp Asn Pro Gly Ile Thr Leu Gln Asn Arg  
1 5 10 15

Lys Thr Lys Glu Gly Pro Arg Ala Pro Pro Ser Arg Met Pro Glu Pro  
20 25 30

Ala Gly Gly Leu Arg Gly Cys Glu Ala Val Gly Thr Leu Leu Met Lys  
35 40 45

Glu Thr Val Phe Ala Leu His Pro Ser Leu Pro Leu Gly Ala Gly Ser  
50 55 60

Ser Pro Ser Ala Thr Cys Ser Glu Gly Leu His Leu Arg Gly Glu Gly  
65 70 75 80

Trp Gly Lys Ser Pro Pro Val Pro Phe Leu Trp Pro Cys Cys Pro His  
85 90 95

Thr Gln Leu Arg Gly Pro Thr Leu Gly Lys Ala Gly Ser Ala Arg Ser  
100 105 110

Leu Ser Pro Ile Ser Ala Leu Ser Ala Trp Ile Pro Ala Glu Ala Met  
115 120 125

525

Lys Gly Asn Lys Glu Lys Arg Xaa Xaa Lys Lys Lys Lys Lys Lys Lys  
130 135 140

Lys Lys Lys Lys Lys Lys Lys Xaa Pro  
145 150

&lt;210&gt; 570

&lt;211&gt; 327

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 570

Pro Gly Ser Pro Arg Arg Cys Asp Ile Ile Ile Ile Ser Gly Arg Lys  
1 5 10 15

Glu Lys Cys Glu Ala Ala Lys Glu Ala Leu Glu Ala Leu Val Pro Val  
20 25 30

Thr Ile Glu Val Glu Val Pro Phe Asp Leu His Arg Tyr Val Ile Gly  
35 40 45

Gln Lys Gly Ser Gly Ile Arg Lys Met Met Asp Glu Phe Glu Val Asn  
50 55 60

Ile His Val Pro Ala Pro Glu Leu Gln Ser Asp Ile Ile Ala Ile Thr  
65 70 75 80

Gly Leu Ala Ala Asn Leu Asp Arg Ala Lys Ala Gly Leu Leu Glu Arg  
85 90 95

Val Lys Glu Leu Gln Ala Glu Gln Glu Asp Arg Ala Leu Arg Ser Phe  
100 105 110

Lys Leu Ser Val Thr Val Asp Pro Lys Tyr His Pro Lys Ile Ile Gly  
115 120 125

Arg Lys Gly Ala Val Ile Thr Gln Ile Arg Leu Glu His Asp Val Asn  
130 135 140

Ile Gln Phe Pro Asp Lys Asp Asp Gly Asn Gln Pro Gln Asp Gln Ile  
145 150 155 160

Thr Ile Thr Gly Tyr Glu Lys Asn Thr Glu Ala Ala Arg Asp Ala Ile  
165 170 175

Leu Arg Ile Val Gly Glu Leu Glu Gln Met Val Ser Glu Asp Val Pro  
180 185 190

Leu Asp His Arg Val His Ala Arg Ile Ile Gly Ala Arg Gly Lys Ala

526

195                      200                      205  
 Ile Arg Lys Ile Met Asp Glu Phe Lys Val Asp Ile Arg Phe Pro Gln  
 210                      215                      220  
 Ser Gly Ala Pro Asp Pro Asn Cys Val Thr Val Thr Gly Leu Pro Glu  
 225                      230                      235                      240  
 Asn Val Glu Glu Ala Ile Asp His Ile Leu Asn Leu Glu Glu Glu Tyr  
 245                      250                      255  
 Leu Ala Asp Val Val Asp Ser Glu Ala Leu Gln Val Tyr Met Lys Pro  
 260                      265                      270  
 Pro Ala His Glu Glu Ala Lys Ala Pro Ser Arg Gly Phe Val Val Arg  
 275                      280                      285  
 Asp Ala Pro Trp Thr Ala Ser Ser Ser Glu Lys Ala Pro Asp Met Ser  
 290                      295                      300  
 Ser Ser Glu Glu Phe Pro Ser Phe Gly Ala Gln Val Ala Pro Lys Thr  
 305                      310                      315                      320  
 Leu Pro Trp Gly Pro Lys Arg  
 325

<210> 571  
 <211> 166  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (9)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (12)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 571  
 Gly Asn Ser Arg Val Asp Pro Arg Xaa Arg Gly Xaa Ala His Thr Cys  
 1                      5                      10                      15  
 Ala Pro Cys Pro Ala Pro Gly Pro Leu Ala Gly Arg Ala Val Ser Gly  
 20                      25                      30  
 His Gly Ser Leu Pro Pro Asp Arg Arg Ala Pro Ser Ala Leu Ser Ser

527

35                      40                      45  
 Pro Ala Asp Glu Gly Glu Arg Arg Arg Pro Asp Leu Asp Glu Ile His  
     50                      55                      60  
 Arg Glu Leu Arg Pro Gln Gly Ser Ala Arg Pro Gln Pro Asp Pro Asn  
     65                      70                      75                      80  
 Ala Glu Phe Asp Pro Asp Leu Pro Gly Gly Gly Leu His Arg Cys Leu  
                     85                      90                      95  
 Ala Cys Ala Arg Tyr Phe Ile Asp Ser Thr Asn Leu Lys Thr His Phe  
                     100                      105                      110  
 Arg Ser Lys Asp His Lys Lys Arg Leu Lys Gln Leu Ser Val Glu Pro  
                     115                      120                      125  
 Tyr Ser Gln Glu Glu Ala Glu Arg Ala Ala Gly Met Gly Ser Tyr Val  
                     130                      135                      140  
 Pro Pro Arg Arg Leu Ala Val Pro Thr Glu Val Ser Thr Glu Val Pro  
     145                      150                      155                      160  
 Glu Met Asp Thr Ser Thr  
                     165

&lt;210&gt; 572

&lt;211&gt; 113

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 572

Gln Ser Ser Thr Phe His Pro Ala Pro Ala Phe Gly Ala Thr Val Ala  
     1                      5                      10                      15  
 Ala Phe His Arg Arg Ala Ala Leu Arg Ala Pro Glu Pro Ala Met Ser  
                     20                      25                      30  
 Gly Pro Asn Gly Asp Leu Gly Met Pro Val Glu Ala Gly Ala Glu Gly  
                     35                      40                      45  
 Glu Glu Asp Gly Phe Gly Glu Ala Glu Tyr Ala Ala Ile Asn Ser Met  
                     50                      55                      60  
 Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys Asn Asp  
     65                      70                      75                      80  
 His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg Gln Thr  
                     85                      90                      95

Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp Ala Ser  
 100 105 110

Pro

<210> 573  
 <211> 99  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (27)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (37)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (38)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 573  
 Gly Ser Gly Ser Ser Arg Asp Leu His Lys Ala Leu Trp Glu Ala Gly  
 1 5 10 15

Trp Glu Thr Val Glu Gly Gly Cys Pro Leu Xaa Pro Arg Arg His Arg  
 20 25 30

Ile Trp Ala Leu Xaa Xaa Ala Phe Leu Pro Glu Tyr Ala Ala Ile Asn  
 35 40 45

Ser Met Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys  
 50 55 60

Asn Asp His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg  
 65 70 75 80

Gln Thr Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp  
 85 90 95

Ala Ser Pro

<210> 574  
 <211> 197  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (97)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (124)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (129)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 574  
 Arg Trp Ala Arg Val Glu Ala Ala Val Met Glu Gly Ala Gly Ala Gly  
 1 5 10 15

Ser Gly Phe Arg Lys Glu Leu Val Ser Arg Leu Leu His Leu His Phe  
 20 25 30

Lys Asp Asp Lys Thr Lys Val Ser Gly Asp Ala Leu Gln Leu Met Val  
 35 40 45

Glu Leu Leu Lys Val Phe Val Val Glu Ala Ala Val Arg Gly Val Arg  
 50 55 60

Gln Ala Gln Ala Glu Asp Ala Leu Arg Val Asp Val Asp Gln Leu Glu  
 65 70 75 80

Lys Val Leu Arg Ser Cys Ser Gly Leu Leu Gly Ile Ser Ala Val Ala  
 85 90 95

Xaa Ala Thr Pro Arg Gly Ala Pro Gly Pro Gln Lys Gln Ala Leu Cys  
 100 105 110

Phe Gln Arg Pro Leu Ile Arg Gly Arg Glu Gly Xaa Glu Gly Phe Gly  
 115 120 125

Xaa Asp Ser Asn Lys Ile Ser Gly Ser Leu Gln Pro Val Gln Lys Gly  
 130 135 140

Gln Asp Cys Ser Ala Leu Arg Ala Leu Glu Cys Pro Val Gly Thr Leu

530

145                      150                      155                      160  
 Val Trp Glu Gly Ala Ala Pro Gly Glu Ser Leu Pro Leu Leu Pro Gly  
                                  165                      170                      175  
 Thr Ile Val Cys Met Pro Pro Gly Val Leu Gln Ala Gly Ala Gly Lys  
                                  180                      185                      190  
 Gly Leu Ala Ser Arg  
                                  195

<210> 575  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 575  
 Leu Pro Met Val Asp Leu Met Glu Lys Leu Asn Ile Phe His Tyr Ala  
   1                                  5                                  10                                  15  
 Leu Gln Asn Thr Val Tyr Val Ser Ala Ser Leu Gly Asn Gly Arg Gly  
                                   20                                  25                                  30  
 Gln Lys Lys Val Thr Phe Asn Leu Cys Ile Phe Ala Lys Pro Tyr  
                                   35                                  40                                  45

<210> 576  
 <211> 115  
 <212> PRT  
 <213> Homo sapiens

<400> 576  
 Trp Ser Arg Thr Ser Gln Pro Leu Pro Ser Thr Val Gly Cys Pro Arg  
   1                                  5                                  10                                  15  
 Arg Arg Gly Phe Lys Asp Phe Gln Arg Arg Ile Leu Val Ala Thr Asn  
                                   20                                  25                                  30  
 Leu Phe Gly Arg Gly Met Asp Ile Glu Arg Val Asn Ile Ala Phe Asn  
                                   35                                  40                                  45  
 Tyr Asp Met Pro Glu Asp Ser Asp Thr Tyr Leu His Arg Val Ala Arg  
                                   50                                  55                                  60  
 Ala Gly Arg Phe Gly Thr Lys Gly Leu Ala Ile Thr Phe Val Ser Asp  
   65                                  70                                  75                                  80



Glu Asn Asp Ala Lys Ile Leu Asn Asp Val Gln Asp Arg Phe Glu Val  
                     85                    90                    95

Asn Ile Ser Glu Leu Pro Asp Glu Ile Asp Ile Ser Ser Tyr Ile Glu  
                     100                    105                    110

Gln Thr Arg  
                     115

<210> 577

<211> 346

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 577

Val Thr Ser Cys Val Ala Leu Leu Pro Ala Arg Arg Met Thr Tyr Thr  
           1                    5                    10                    15

Thr Glu Thr Ala Leu Leu Asn Trp Ser Thr Cys Gln Met Val Leu Arg  
                     20                    25                    30

Gly Ala Glu Thr Xaa Gly Cys Val Ile Val Ser Ala Ala Lys Ala Gln  
           35                    40                    45

Leu Leu Gln Cys Gln His His Pro Ala Trp Tyr Gly Asp Thr Leu Lys  
           50                    55                    60

Gln Lys Thr Ser Trp Thr Cys Leu Leu Asp Gly Met Gln Tyr Phe Ala  
           65                    70                    75                    80

Thr Thr Glu Ser Ser Pro Thr Glu Gln Asp Gly Arg Gln Leu Trp Leu  
                     85                    90                    95

Glu Val Lys Asn Ile Glu Glu His Arg Gln Arg Ser Leu Asp Ser Val  
                     100                    105                    110

Gln Glu Leu Met Glu Ser Gly Gln Ala Val Gly Gly Met Val Thr Thr  
           115                    120                    125

Thr Thr Asp Trp Asn Gln Pro Ala Glu Ala Gln Gln Ala Gln Gln Val  
           130                    135                    140

Gln Arg Ile Ile Ser Arg Cys Asn Cys Arg Met Tyr Tyr Ile Ser Tyr  
           145                    150                    155                    160

Ser His Asp Ile Asp Pro Glu Leu Ala Thr Gln Ile Lys Pro Pro Glu  
 165 170 175  
 Val Leu Glu Asn Gln Glu Lys Glu Asp Leu Leu Lys Lys Gln Glu Gly  
 180 185 190  
 Ala Val Asp Thr Phe Thr Leu Ile His His Glu Leu Glu Ile Ser Thr  
 195 200 205  
 Asn Pro Ala Gln Tyr Ala Met Ile Leu Asp Ile Val Asn Asn Leu Leu  
 210 215 220  
 Leu His Val Glu Pro Lys Arg Lys Glu His Ser Glu Lys Lys Gln Arg  
 225 230 235 240  
 Val Arg Phe Gln Leu Glu Ile Ser Ser Asn Pro Glu Glu Gln Arg Ser  
 245 250 255  
 Ser Ile Leu His Leu Gln Glu Ala Val Arg Gln His Val Ala Gln Ile  
 260 265 270  
 Arg Gln Leu Glu Lys Gln Met Tyr Ser Ile Met Lys Ser Leu Gln Asp  
 275 280 285  
 Asp Ser Lys Asn Glu Asn Leu Leu Asp Leu Asn Gln Lys Leu Gln Leu  
 290 295 300  
 Gln Leu Asn Gln Glu Lys Ala Asn Leu Gln Leu Glu Ser Glu Glu Leu  
 305 310 315 320  
 Asn Ile Leu Ile Arg Cys Phe Lys Asp Phe Gln Leu Gln Arg Ala Asn  
 325 330 335  
 Lys Met Glu Leu Arg Lys His Lys Lys Met  
 340 345

&lt;210&gt; 578

&lt;211&gt; 91

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 578

Arg His Glu Gly His Leu Gly Ser Gly Arg Asn Gly Gly Gly Ser Met  
 1 5 10 15  
 Asn Ala Pro Pro Ala Phe Glu Ser Phe Leu Leu Phe Glu Gly Glu Lys  
 20 25 30

Ile Thr Ile Asn Lys Asp Thr Lys Val Pro Asn Ala Cys Leu Phe Thr  
35 40 45

Ile Asn Lys Glu Asp His Thr Leu Gly Asn Ile Ile Lys Ser Arg Ala  
50 55 60

Cys Phe Pro Phe Ala Phe Cys Arg Asp Cys Gln Phe Pro Glu Ala Ser  
65 70 75 80

Pro Ala Thr Leu Pro Val Gln Pro Ala Glu Leu  
85 90

<210> 579  
<211> 331  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (18)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (20)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (300)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (311)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (313)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (320)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE

&lt;222&gt; (325)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 579

Gly Arg Pro Thr Arg Pro Gly Gly Leu Gly Ser Gly Val Leu Ala Leu  
 1 5 10 15

Ala Xaa Gly Xaa Pro Ala Arg Leu Ala Gly Thr Val His Glu Val Gly  
 20 25 30

Asp Ala Pro Arg Arg Ala Pro Asp Gln Ala Ala Glu Ile Gly Ser Arg  
 35 40 45

Gly Ser Thr Lys Ala Gln Gly Pro Gln Gln Gln Pro Gly Ser Glu Gly  
 50 55 60

Pro Ser Tyr Ala Lys Lys Val Ala Leu Trp Leu Ala Gly Leu Leu Gly  
 65 70 75 80

Ala Gly Gly Thr Val Ser Val Val Tyr Ile Phe Gly Asn Asn Pro Val  
 85 90 95

Asp Glu Asn Gly Ala Lys Ile Pro Asp Glu Phe Asp Asn Asp Pro Ile  
 100 105 110

Leu Val Gln Gln Leu Arg Arg Thr Tyr Lys Tyr Phe Lys Asp Tyr Arg  
 115 120 125

Gln Met Ile Ile Glu Pro Thr Ser Pro Cys Leu Leu Pro Asp Pro Leu  
 130 135 140

Gln Glu Pro Tyr Tyr Gln Pro Pro Tyr Thr Leu Val Leu Glu Leu Thr  
 145 150 155 160

Gly Val Leu Leu His Pro Glu Trp Ser Leu Ala Thr Gly Trp Arg Phe  
 165 170 175

Lys Lys Arg Pro Gly Ile Glu Thr Leu Phe Gln Gln Leu Ala Pro Leu  
 180 185 190

Tyr Glu Ile Val Ile Phe Thr Ser Glu Thr Gly Met Thr Ala Phe Pro  
 195 200 205

Leu Ile Asp Ser Val Asp Pro His Gly Phe Ile Ser Tyr Arg Leu Phe  
 210 215 220

Arg Asp Ala Thr Arg Tyr Met Asp Gly His His Val Lys Asp Ile Ser  
 225 230 235 240

Cys Leu Asn Arg Asp Pro Ala Arg Val Val Val Val Asp Cys Lys Lys  
 245 250 255

Glu Ala Phe Arg Leu Gln Pro Tyr Asn Gly Val Ala Leu Arg Pro Trp  
260 265 270

Asp Gly Asn Ser Asp Asp Arg Val Leu Leu Asp Leu Ser Ala Phe Leu  
275 280 285

Lys Thr Ile Ala Leu Asn Gly Val Gly Gly Arg Xaa Glu Pro Cys Trp  
290 295 300

Glu His Tyr Ala Leu Gly Xaa Asp Xaa Pro Arg Trp Ala Ala Phe Xaa  
305 310 315 320

Asn Ser Gly Lys Xaa Gly Leu Glu Ala Gly Arg  
325 330

<210> 580

<211> 374

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (285)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (307)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (319)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (324)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (341)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (359)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 580

Pro Ser Thr Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Pro Arg  
1 5 10 15

Val Arg Ala Gly Val Ala Ala Leu Ala Thr Val Gly Val Ala Ser Gly  
20 25 30

Pro Gly Pro Gly Arg Pro Gly Pro Leu Gln Asp Glu Thr Leu Gly Val  
35 40 45

Ala Ser Val Pro Ser Gln Trp Arg Ala Val Gln Gly Ile Arg Gly Glu  
50 55 60

Thr Lys Ser Cys Gln Thr Ala Ser Ile Ala Thr Ala Ser Ala Ser Ala  
65 70 75 80

Gln Ala Arg Asn His Val Asp Ala Gln Val Gln Thr Glu Ala Pro Val  
85 90 95

Pro Val Ser Val Gln Pro Pro Ser Gln Tyr Asp Ile Pro Arg Leu Ala  
100 105 110

Ala Phe Leu Arg Arg Val Glu Ala Met Val Ile Arg Glu Leu Asn Lys  
115 120 125

Asn Trp Gln Ser His Ala Phe Asp Gly Phe Glu Val Asn Trp Thr Glu  
130 135 140

Gln Gln Gln Met Val Ser Cys Leu Tyr Thr Leu Gly Tyr Pro Pro Ala  
145 150 155 160

Gln Ala Gln Gly Leu His Val Thr Ser Ile Ser Trp Asn Ser Thr Gly  
165 170 175

Ser Val Val Ala Cys Ala Tyr Gly Arg Leu Asp His Gly Asp Trp Ser  
180 185 190

Thr Leu Lys Ser Phe Val Cys Ala Trp Asn Leu Asp Arg Arg Asp Leu  
195 200 205

Arg Pro Gln Gln Pro Ser Ala Val Val Glu Val Pro Ser Ala Val Leu  
210 215 220

Cys Leu Ala Phe His Pro Thr Gln Pro Ser Xaa Val Ala Gly Gly Leu

537

225                      230                      235                      240  
 Tyr Ser Gly Glu Val Leu Val Trp Asp Leu Ser Arg Leu Glu Asp Pro  
                                  245                      250                      255  
 Leu Leu Trp Arg Thr Gly Leu Thr Asp Asp Thr His Thr Asp Pro Val  
                                  260                      265                      270  
 Ser Gln Val Val Trp Leu Pro Glu Pro Gly His Ser Xaa Arg Phe Gln  
                                  275                      280                      285  
 Val Leu Ser Val Ala Thr Asp Gly Lys Val Leu Leu Trp Gln Gly Ile  
                                  290                      295                      300  
 Gly Val Xaa Gln Leu Gln Phe Thr Glu Gly Phe Ala Trp Phe Xaa Gln  
 305                                   310                                   315                                   320  
 Gln Leu Pro Xaa Ser Thr Lys Leu Lys Lys His Pro Arg Gly Arg Pro  
                                  325                                   330                                   335  
 Arg Trp Ala Pro Xaa Gln Ala Phe Phe Gln Phe Asp Leu Arg Phe Ser  
                                  340                                   345                                   350  
 Phe Trp Gln Glu Ala Val Xaa Val Gln Phe Ser Trp His Trp Arg Ala  
                                  355                                   360                                   365  
 Ala Leu Arg Gly Ala His  
 370

&lt;210&gt; 581

&lt;211&gt; 94

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (90)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 581

Cys Pro Asp Gln Asn Gly Trp Ala Ser Phe Gly Ala Pro Leu Ser Ala  
 1                                   5                                   10                                   15

Gly Gly Gln Pro Cys Tyr Leu Leu Asp Ile Gly Cys Gly Ser Gly Leu

```

                20                25                30
Ser Gly Asp Tyr Leu Ser Asp Glu Gly His Tyr Trp Val Gly Ile Asp
   35                40                45

Ile Ser Pro Ala Met Leu Asp Ala Ala Leu Asp Arg Asp Thr Glu Gly
   50                55                60

Asp Leu Leu Leu Gly Asp Met Gly Gln Gly Ile Pro Phe Lys Pro Xaa
   65                70                75                80

Ser Leu Met Asp Val Ser Ala Phe Cys Xaa Ser Val Ala Leu
   85                90

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<210> 582  
 <211> 163  
 <212> PRT  
 <213> Homo sapiens

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<400> 582
Pro Thr Arg Pro Ala Ala Gly Gly Ala Glu Arg Ile Ala Gly Ser Ala
   1                5                10                15

Met Ser Ser Glu Pro Pro Pro Pro Pro Gln Pro Pro Thr His Gln Ala
   20                25                30

Ser Val Gly Leu Leu Asp Thr Pro Arg Ser Arg Glu Arg Ser Pro Ser
   35                40                45

Pro Leu Arg Gly Asn Val Val Pro Ser Pro Leu Pro Thr Arg Arg Thr
   50                55                60

Arg Thr Phe Ser Ala Thr Val Arg Ala Ser Gln Gly Pro Val Tyr Lys
   65                70                75                80

Gly Val Cys Lys Cys Phe Cys Arg Ser Lys Gly His Gly Phe Ile Thr
   85                90                95

Pro Ala Asp Gly Gly Pro Asp Ile Phe Leu His Ile Ser Asp Val Glu
  100                105                110

Gly Glu Tyr Val Pro Val Glu Gly Asp Glu Val Thr Tyr Lys Met Cys
  115                120                125

Ser Ile Pro Pro Lys Asn Glu Lys Leu Gln Ala Val Glu Val Val Ile
  130                135                140

Thr His Leu Ala Pro Gly Thr Lys His Glu Thr Trp Ser Gly His Val
  145                150                155                160

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Ile Ser Ser

<210> 583

<211> 293

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (52)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (53)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (58)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (150)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (171)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (207)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (254)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 583

Leu Leu Gly Pro Asn Leu Thr Met Gly Ser Gln Pro Gly Arg Ile Pro  
1 5 10 15

Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr

540

20					25					30					
Ile	Asp	Val	Tyr	Met	Ile	Met	Val	Lys	Cys	Trp	Met	Ile	Asp	Ser	Glu
	35						40					45			
Cys	Arg	Pro	Xaa	Xaa	Arg	Glu	Leu	Val	Xaa	Glu	Phe	Ser	Arg	Met	Ala
	50					55					60				
Arg	Asp	Pro	Gln	Arg	Phe	Val	Val	Ile	Gln	Asn	Glu	Asp	Leu	Gly	Pro
	65					70					75				80
Ala	Ser	Pro	Leu	Asp	Ser	Thr	Phe	Tyr	Arg	Ser	Leu	Leu	Glu	Asp	Asp
				85					90					95	
Asp	Met	Gly	Asp	Leu	Val	Asp	Ala	Glu	Glu	Tyr	Leu	Val	Pro	Gln	Gln
		100					105					110			
Gly	Phe	Phe	Cys	Pro	Asp	Pro	Ala	Pro	Gly	Ala	Gly	Gly	Met	Val	His
		115					120					125			
His	Arg	His	Arg	Ser	Ser	Ser	Thr	Arg	Ser	Gly	Gly	Gly	Asp	Leu	Thr
	130					135						140			
Leu	Gly	Leu	Glu	Pro	Xaa	Glu	Arg	Gly	Gly	Pro	Gln	Val	Ser	Thr	Gly
	145					150					155				160
Thr	Leu	Arg	Arg	Ala	Gly	Ser	Asp	Val	Phe	Xaa	Gly	Asp	Leu	Gly	Met
				165					170					175	
Gly	Ala	Ala	Lys	Gly	Leu	Gln	Ser	Leu	Pro	Thr	His	Asp	Pro	Ser	Pro
			180					185					190		
Leu	Gln	Arg	Tyr	Ser	Glu	Asp	Pro	Thr	Val	Pro	Leu	Pro	Ser	Xaa	Thr
		195					200					205			
Asp	Gly	Tyr	Val	Ala	Pro	Leu	Thr	Cys	Ser	Pro	Gln	Pro	Glu	Tyr	Val
	210					215					220				
Asn	Gln	Pro	Asp	Val	Arg	Pro	Gln	Pro	Pro	Ser	Pro	Arg	Glu	Gly	Pro
	225					230					235				240
Leu	Pro	Ala	Ala	Arg	Pro	Ala	Gly	Ala	Thr	Leu	Glu	Arg	Xaa	Lys	Thr
				245					250					255	
Leu	Ser	Pro	Gly	Lys	Asn	Gly	Val	Val	Lys	Glu	Phe	Leu	Pro	Leu	Gly
		260						265					270		
Val	Pro	Trp	Arg	Thr	Pro	Ser	Ile	Asp	Thr	Pro	Gly	Glu	Gly	Ala	Cys
		275					280						285		
Pro	Ser	Ala	Pro	Pro											

290

&lt;210&gt; 584

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 584

Gly Gly Ala Gln Pro Gly Met Glu Gly Ala Ala Ala Thr Val His Leu  
1 5 10 15

Ile Ser Gln Trp Ala Val Glu Pro Asn Ala Arg Val Gly Pro Leu Leu  
20 25 30

Glu Val Glu Ala Ala Ala Ala Asp His His Glu Ala Ala Ala Gly Ala  
35 40 45

Gly Ser Ala Val Glu Lys Ile Cys Ile Asp Lys Gly Leu Thr Asp Glu  
50 55 60

Ser Glu Ile Leu Arg Phe Leu Gln His Gly Thr Leu Val Gly Leu Leu  
65 70 75 80

Pro Val Pro His Pro Ile Leu Ile Arg Lys Tyr Gln Ala Asn Ser Gly  
85 90 95

Thr Ala Met Trp Phe Arg Thr Tyr Met Trp Gly Val Ile Tyr Leu Arg  
100 105 110

Asn Val Asp Pro Pro Val Trp Tyr Asp Thr Asp Val Lys Leu Phe Glu  
115 120 125

Ile Gln Arg Val  
130

&lt;210&gt; 585

&lt;211&gt; 218

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (54)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

<222> (92)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (117)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (140)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (141)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (188)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (199)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <220>  
 <221> SITE  
 <222> (200)  
 <223> Xaa equals any of the naturally occurring L-amino acids  
  
 <400> 585  
 Arg Glu Arg Cys Arg Arg Glu Ala Leu Arg Gly Ser Arg Leu Cys Pro  
   1                  5                  10                  15  
  
 Ala Thr Pro Pro Ser Ala Leu Gly Ser Gln Asp Gly Ser Arg Thr Arg  
                   20                  25                  30  
  
 Asp Arg Leu Gly Ala Ala Gly Trp Pro Gly Leu Val Val Gly Leu Cys  
           35                  40                  45  
  
 Thr Pro Ala Ala Gly Xaa Gln Arg Asp Leu Leu His Arg Arg Gly Gly  
   50                  55                  60  
  
 Thr Ala Ser Phe Gly Lys Ser Phe Ala Gln Lys Ser Gly Tyr Phe Leu  
   65                  70                  75                  80  
  
 Cys Leu Ser Ser Leu Gly Ser Leu Glu Asn Pro Xaa Glu Asn Val Val  
           85                  90                  95

Ala Asp Ile Gln Ile Val Val Asp Lys Ser Pro Leu Pro Leu Gly Phe  
 100 105 110

Ser Pro Val Cys Xaa Pro Met Asp Ser Lys Ala Ser Val Ser Lys Lys  
 115 120 125

Lys Arg Met Cys Val Lys Leu Leu Pro Leu Gly Xaa Xaa Asp Thr Ala  
 130 135 140

Val Phe Asp Val Arg Leu Ser Gly Lys Thr Lys Thr Val Pro Gly Tyr  
 145 150 155 160

Leu Arg Ile Gly Asp Met Gly Gly Phe Ala Ile Trp Cys Lys Lys Gly  
 165 170 175

Gln Gly Pro Glu Ala Ser Cys Pro Lys Pro Arg Xaa Pro Gln Pro Gly  
 180 185 190

Thr Cys Lys Gly Phe Ser Xaa Xaa Ala Ala Ser Gln Pro Lys Leu Arg  
 195 200 205

Ala Gly Leu Leu Gly Ser Arg Thr Ser Val  
 210 215

&lt;210&gt; 586

&lt;211&gt; 233

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 586

Ala Arg Gly Glu Met Glu Gly Arg Gln Val Leu Glu Val Lys Met Gln  
 1 5 10 15

Val Glu Tyr Met Ser Phe Ser Ala His Ala Asp Ala Lys Gly Ile Met  
 20 25 30

Gln Leu Val Gly Gln Ala Glu Pro Xaa Ser Val Leu Leu Val His Gly  
 35 40 45

Glu Ala Lys Lys Met Glu Phe Leu Lys Gln Lys Ile Glu Gln Glu Leu  
 50 55 60

Arg Val Asn Cys Tyr Met Pro Ala Asn Gly Glu Thr Val Thr Leu Pro

65                      70                      75                      80  
 Thr Ser Pro Ser Ile Pro Val Gly Ile Ser Leu Gly Leu Leu Lys Arg  
                                  85                      90                      95  
 Glu Met Ala Gln Gly Leu Leu Pro Glu Ala Lys Lys Pro Arg Leu Leu  
                                  100                      105                      110  
 His Gly Thr Leu Ile Met Lys Asp Ser Asn Phe Arg Leu Val Ser Ser  
                                  115                      120                      125  
 Glu Gln Ala Leu Lys Glu Leu Gly Leu Ala Glu His Gln Leu Arg Phe  
                                  130                      135                      140  
 Thr Cys Arg Val His Leu His Asp Thr Arg Lys Glu Gln Glu Thr Ala  
 145                      150                      155                      160  
 Leu Arg Val Tyr Ser His Leu Lys Ser Val Leu Lys Asp His Cys Val  
                                  165                      170                      175  
 Gln His Leu Pro Asp Gly Ser Val Thr Val Glu Ser Val Leu Leu Gln  
                                  180                      185                      190  
 Ala Ala Ala Pro Ser Glu Asp Pro Gly Thr Lys Val Leu Leu Val Ser  
                                  195                      200                      205  
 Trp Thr Tyr Gln Asp Glu Glu Leu Gly Ser Phe Leu Thr Ser Leu Leu  
                                  210                      215                      220  
 Lys Lys Gly Leu Pro Gln Ala Pro Ser  
 225                      230

&lt;210&gt; 587

&lt;211&gt; 116

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (100)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 587

Gly Pro Leu Ser His His Ile Arg Ala Gln Leu Ser Lys Met Leu Leu  
   1                                  5                                  10                                  15  
 Ala Arg Lys Gln Ile Leu Cys Val Asn Val Lys Asn Phe Ala Val Ile  
                                   20                                  25                                  30

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<210> 588
<211> 133
<212> PRT
<213> Homo sapiens
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<400>	588
Ala Arg Ala Ala Val Gly Arg Thr Ala Gly Val Arg Thr Trp Ala Pro	
1                  5                  10                  15	
Leu Ala Met Ala Ala Lys Val Asp Leu Ser Thr Ser Thr Asp Trp Lys	
20                  25                  30	
Glu Ala Lys Ser Phe Leu Lys Gly Leu Ser Asp Lys Gln Arg Glu Glu	
35                  40                  45	
His Tyr Phe Cys Lys Asp Phe Val Arg Leu Lys Lys Ile Pro Thr Trp	
50                  55                  60	
Lys Glu Met Ala Lys Gly Val Ala Val Lys Val Glu Glu Pro Arg Tyr	
65                  70                  75                  80	
Lys Lys Asp Lys Gln Leu Asn Glu Lys Ile Ser Leu Leu Arg Ser Asp	
85                  90                  95	
Ile Thr Lys Leu Glu Val Asp Ala Ile Val Asn Ala Ala Asn Ser Ser	
100                  105                  110	
Pro Pro Pro Arg Ser Leu Ile Lys Asp Leu Arg Cys Gly Lys Lys Lys	
115                  120                  125	
Lys Lys Lys Lys Lys	

130

&lt;210&gt; 589

&lt;211&gt; 163

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 589

Arg His Arg Gly Gln Pro Leu Arg Gln Thr Arg Ala Ser Ser Ser Pro  
 1 5 10 15

Gln Leu Ala Gly Arg Ser Ser Ser Val Leu Pro Ala Ala Ala Gln Pro  
 20 25 30

Cys Thr Pro Thr Met Asp Val Phe Lys Lys Gly Phe Ser Ile Ala Lys  
 35 40 45

Glu Gly Val Val Gly Ala Val Glu Lys Thr Lys Gln Gly Val Thr Glu  
 50 55 60

Ala Ala Glu Lys Thr Lys Glu Gly Val Met Tyr Val Gly Ala Lys Thr  
 65 70 75 80

Lys Glu Asn Val Val Gln Ser Val Thr Ser Val Ala Glu Lys Thr Lys  
 85 90 95

Glu Gln Ala Asn Ala Val Ser Glu Ala Val Val Ser Ser Val Asn Thr  
 100 105 110

Val Ala Thr Lys Thr Val Glu Glu Ala Glu Asn Ile Ala Val Thr Ser  
 115 120 125

Gly Val Val Arg Lys Glu Asp Leu Arg Pro Ser Ala Pro Gln Gln Glu  
 130 135 140

Gly Glu Ala Ser Lys Glu Lys Glu Glu Val Ala Glu Glu Ala Gln Ser  
 145 150 155 160

Gly Gly Asp

&lt;210&gt; 590

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 590



Arg Ala Leu Leu Cys Leu Gly His His Pro Leu Leu Ala Gln Gly Val  
 1 5 10 15  
 Pro Ala Leu Ser Asp Met Arg Leu Pro Thr Leu Leu Pro Ser Ser Pro  
 20 25 30  
 Trp Pro Pro Leu Ala Cys Pro Pro Val Leu Leu His Gln Pro His Cys  
 35 40 45  
 Pro Pro Ser Ala Pro Pro Thr Leu Trp Ser Phe  
 50 55

&lt;210&gt; 591

&lt;211&gt; 116

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 591

Val His Ala Glu Ala Gly Arg Leu Cys His Gly Asp Cys Pro Arg Leu  
 1 5 10 15  
 Cys Arg Pro Arg Gln Arg Ser Ala Pro Val Gln Val Tyr Thr Xaa Arg  
 20 25 30  
 Gln Ala Ala Leu His Gly Arg Pro Gln Arg Asp Pro Cys Val Gly Gly  
 35 40 45  
 Pro Arg Pro Leu Arg Cys Ser Arg Asp Cys Gly Gly Gly His Gln Arg  
 50 55 60  
 Leu Val Met Pro Gly Thr Trp Thr Gln Ala Trp Gln Arg Arg Gln Val  
 65 70 75 80  
 Val Asn Gly Leu Met Leu Gly Gln Ala Arg Ile His Val Asn Arg Leu  
 85 90 95  
 Glu Gln Ala Val Val Asn Leu Ala Pro Cys Glu Tyr Phe His Thr Cys  
 100 105 110  
 Cys Pro Phe Ala  
 115

<210> 592  
 <211> 290  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (30)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (239)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 592

Arg	Arg	Ser	Leu	Asn	Thr	His	Gly	Ser	Gly	Val	Ser	Val	Cys	Leu	Gln
1				5					10					15	
Ser	Leu	Thr	Leu	Leu	Ala	Thr	Leu	Cys	Pro	Gly	Asp	Gln	Xaa	Ser	Leu
			20					25						30	
Gly	Leu	Leu	Thr	Pro	Cys	Tyr	Ser	Gly	Ser	Glu	Pro	Ser	Gly	Thr	Phe
		35					40					45			
Gly	Pro	Val	Asn	Pro	Ser	Leu	Asn	Asn	Thr	Tyr	Glu	Phe	Met	Ser	Thr
		50				55						60			
Phe	Phe	Leu	Glu	Val	Ser	Ser	Val	Phe	Pro	Asp	Phe	Tyr	Leu	His	Leu
65					70					75				80	
Gly	Gly	Asp	Glu	Val	Asp	Phe	Thr	Cys	Trp	Lys	Ser	Asn	Pro	Glu	Ile
			85						90					95	
Gln	Asp	Phe	Met	Arg	Lys	Lys	Gly	Phe	Gly	Glu	Asp	Phe	Lys	Gln	Leu
			100					105					110		
Glu	Ser	Phe	Tyr	Ile	Gln	Thr	Leu	Leu	Asp	Ile	Val	Ser	Ser	Tyr	Gly
		115					120						125		
Lys	Gly	Tyr	Val	Val	Trp	Gln	Glu	Val	Phe	Asp	Asn	Lys	Val	Lys	Ile
		130				135					140				
Gln	Pro	Asp	Thr	Ile	Ile	Gln	Val	Trp	Arg	Glu	Asp	Ile	Pro	Val	Asn
145					150					155				160	
Tyr	Met	Lys	Glu	Leu	Glu	Leu	Val	Thr	Lys	Ala	Gly	Phe	Arg	Ala	Leu
			165						170					175	
Leu	Ser	Ala	Pro	Trp	Tyr	Leu	Asn	Arg	Ile	Ser	Tyr	Gly	Pro	Asp	Trp
			180					185					190		

Lys Asp Phe Tyr Val Val Glu Pro Leu Ala Phe Glu Gly Thr Pro Glu  
195 200 205

Gln Lys Ala Leu Val Ile Gly Gly Glu Ala Cys Met Trp Gly Glu Tyr  
210 215 220

Val Asp Asn Thr Asn Leu Val Pro Arg Leu Trp Pro Arg Ala Xaa Ala  
225 230 235 240

Val Ala Glu Arg Leu Trp Ser Asn Lys Leu Thr Ser Asp Leu Thr Phe  
245 250 255

Ala Tyr Glu Arg Leu Ser His Phe Arg Cys Glu Leu Leu Arg Arg Gly  
260 265 270

Val Gln Ala Gln Pro Leu Asn Val Gly Phe Cys Glu Gln Glu Phe Glu  
275 280 285

Gln Thr  
290

<210> 593

<211> 665

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 593

Asp Ala Asp Gly Arg Met Asp Xaa Leu Val Ser Glu Cys Ser Ala Arg  
1 5 10 15

Leu Leu Gln Gln Glu Glu Glu Ile Lys Ser Leu Thr Ala Glu Ile Asp  
20 25 30

Arg Leu Lys Asn Cys Gly Cys Leu Gly Ala Ser Pro Asn Leu Glu Gln  
35 40 45

Leu Gln Glu Glu Asn Leu Lys Leu Lys Tyr Arg Leu Asn Ile Leu Arg  
50 55 60

Lys Ser Leu Gln Ala Glu Arg Asn Lys Pro Thr Lys Asn Met Ile Asn  
65 70 75 80

Ile Ile Ser Arg Leu Gln Glu Val Phe Gly His Ala Ile Lys Ala Ala

550

85					90					95					
Tyr	Pro	Asp	Leu	Glu	Asn	Pro	Pro	Leu	Leu	Val	Thr	Pro	Ser	Gln	Gln
			100					105					110		
Ala	Lys	Phe	Gly	Asp	Tyr	Gln	Cys	Asn	Ser	Ala	Met	Gly	Ile	Ser	Gln
			115				120					125			
Met	Leu	Lys	Thr	Lys	Glu	Gln	Lys	Val	Asn	Pro	Arg	Glu	Ile	Ala	Glu
			130				135					140			
Asn	Ile	Thr	Lys	His	Leu	Pro	Asp	Asn	Glu	Cys	Ile	Glu	Lys	Val	Glu
					150					155					160
Ile	Ala	Gly	Pro	Gly	Phe	Ile	Asn	Val	His	Leu	Arg	Lys	Asp	Phe	Val
					165				170					175	
Ser	Glu	Gln	Leu	Thr	Ser	Leu	Leu	Val	Asn	Gly	Val	Gln	Leu	Pro	Ala
			180					185					190		
Leu	Gly	Glu	Asn	Lys	Lys	Val	Ile	Val	Asp	Phe	Ser	Ser	Pro	Asn	Ile
			195				200					205			
Ala	Lys	Glu	Met	His	Val	Gly	His	Leu	Arg	Ser	Thr	Ile	Ile	Gly	Glu
			210				215					220			
Ser	Ile	Ser	Arg	Leu	Phe	Glu	Phe	Ala	Gly	Tyr	Asp	Val	Leu	Arg	Leu
			225			230				235				240	
Asn	His	Val	Gly	Asp	Trp	Gly	Thr	Gln	Phe	Gly	Met	Leu	Ile	Ala	His
					245				250					255	
Leu	Gln	Asp	Lys	Phe	Pro	Asp	Tyr	Leu	Thr	Val	Ser	Pro	Pro	Ile	Gly
			260					265					270		
Asp	Leu	Gln	Val	Phe	Tyr	Lys	Glu	Ser	Lys	Lys	Arg	Phe	Asp	Thr	Glu
			275				280					285			
Glu	Glu	Phe	Lys	Lys	Arg	Ala	Tyr	Gln	Cys	Val	Val	Leu	Leu	Gln	Gly
			290				295					300			
Lys	Asn	Pro	Asp	Ile	Thr	Lys	Ala	Trp	Lys	Leu	Ile	Cys	Asp	Val	Ser
			305				310					315			320
Arg	Gln	Glu	Leu	Asn	Lys	Ile	Tyr	Asp	Ala	Leu	Asp	Val	Ser	Leu	Ile
					325				330					335	
Glu	Arg	Gly	Glu	Ser	Phe	Tyr	Gln	Asp	Arg	Met	Asn	Asp	Ile	Val	Lys
			340					345					350		
Glu	Phe	Glu	Asp	Arg	Gly	Phe	Val	Gln	Val	Asp	Asp	Gly	Arg	Lys	Ile

355	360	365
Val Phe Val Pro Gly Cys Ser Ile Pro Leu Thr Ile Val Lys Ser Asp		
370	375	380
Gly Gly Tyr Thr Tyr Asp Thr Ser Asp Leu Ala Ala Ile Lys Gln Arg		
385	390	400
Leu Phe Glu Glu Lys Ala Asp Met Ile Ile Tyr Val Val Asp Asn Gly		
	405	410 415
Gln Ser Val His Phe Gln Thr Ile Phe Ala Ala Ala Gln Met Ile Gly		
	420	425 430
Trp Tyr Asp Pro Lys Val Thr Arg Val Phe His Ala Gly Phe Gly Val		
	435	440 445
Val Leu Gly Glu Asp Lys Lys Lys Phe Lys Thr Arg Ser Gly Glu Thr		
	450	455 460
Val Arg Leu Met Asp Leu Leu Gly Glu Gly Leu Lys Arg Ser Met Asp		
	465	470 475 480
Lys Leu Lys Glu Lys Glu Arg Asp Lys Val Leu Thr Ala Glu Glu Leu		
	485	490 495
Asn Ala Ala Gln Thr Ser Val Ala Tyr Gly Cys Ile Lys Tyr Ala Asp		
	500	505 510
Leu Ser His Asn Arg Leu Asn Asp Tyr Ile Phe Ser Phe Asp Lys Met		
	515	520 525
Leu Asp Asp Arg Gly Asn Thr Ala Ala Tyr Leu Leu Tyr Ala Phe Thr		
	530	535 540
Arg Ile Arg Ser Ile Ala Arg Leu Ala Asn Ile Asp Glu Glu Met Leu		
	545	550 555 560
Gln Lys Ala Ala Arg Glu Thr Lys Ile Leu Leu Asp His Glu Lys Glu		
	565	570 575
Trp Lys Leu Gly Arg Cys Ile Leu Arg Phe Pro Glu Ile Leu Gln Lys		
	580	585 590
Ile Leu Asp Asp Leu Phe Leu His Thr Leu Cys Asp Tyr Ile Tyr Glu		
	595	600 605
Leu Ala Thr Ala Phe Thr Glu Phe Tyr Asp Ser Cys Tyr Cys Val Glu		
	610	615 620
Lys Asp Arg Gln Thr Gly Lys Ile Leu Lys Val Asn Met Trp Arg Met		

625                      630                      635                      640  
 Leu Leu Cys Glu Ala Val Ala Ala Val Met Ala Lys Gly Phe Asp Ile  
                                 645                      650                      655

Leu Gly Ile Lys Pro Val Gln Arg Met  
                                 660                      665

<210> 594  
 <211> 116  
 <212> PRT  
 <213> Homo sapiens

<400> 594  
 Thr Val Thr Glu Thr Thr Val Thr Val Thr Thr Glu Pro Glu Asn Arg  
     1                      5                      10                      15  
 Ser Leu Thr Ile Lys Leu Arg Lys Arg Lys Pro Glu Lys Lys Val Glu  
                                 20                      25                      30  
 Trp Thr Ser Asp Thr Val Asp Asn Glu His Met Gly Arg Arg Ser Ser  
                                 35                      40                      45  
 Lys Cys Cys Cys Ile Tyr Glu Lys Pro Arg Ala Phe Gly Glu Ser Ser  
                                 50                      55                      60  
 Thr Glu Ser Asp Glu Glu Glu Glu Gly Cys Gly His Thr His Cys  
     65                      70                      75                      80  
 Val Arg Gly His Arg Lys Gly Arg Arg Arg Ala Thr Leu Gly Pro Thr  
                                 85                      90                      95  
 Pro Thr Thr Pro Pro Gln Pro Pro Asp Pro Ser Gln Pro Pro Pro Gly  
                                 100                      105                      110  
 Pro Met Gln His  
                                 115

<210> 595  
 <211> 294  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (269)  
 <223> Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (278)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 595

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Thr Gln Leu Arg Val Ser Glu Arg Glu Gly Pro Gly Asp Pro Gln Arg
 1           5           10           15

Phe Ser Asp His Thr Leu Arg Thr Pro Arg Leu Glu Asp Arg Pro Gly
          20           25           30

Asp Ala Met Trp Gly Glu Gly Leu Arg Ala Trp Cys Arg Phe Val Glu
      35           40           45

Asn Arg Trp Cys Leu Lys Arg Val Ser Ala Pro Leu His Leu Gly Leu
      50           55           60

Leu Gly Cys Pro Asp Ala Glu Ala His Phe Pro Ala Met Leu Thr Leu
      65           70           75           80

Pro Leu Ser Pro Pro Ser Arg Lys Met Ala Thr Asn Phe Leu Ala His
          85           90           95

Glu Lys Ile Trp Phe Asp Lys Phe Lys Tyr Asp Asp Ala Glu Arg Arg
      100           105           110

Phe Tyr Glu Gln Met Asn Gly Pro Val Ala Gly Ala Ser Arg Gln Glu
      115           120           125

Asn Gly Ala Ser Val Ile Leu Arg Asp Ile Ala Arg Ala Arg Glu Asn
      130           135           140

Ile Gln Lys Ser Leu Ala Gly Ser Ser Gly Pro Gly Ala Ser Ser Gly
      145           150           155           160

Thr Ser Gly Asp His Gly Glu Leu Val Val Arg Ile Ala Ser Leu Glu
          165           170           175

Val Glu Asn Gln Ser Leu Arg Gly Val Val Gln Glu Leu Gln Gln Ala
      180           185           190

Ile Ser Lys Leu Glu Ala Arg Leu Asn Val Leu Glu Lys Ser Ser Pro
      195           200           205

Gly His Arg Ala Thr Ala Pro Gln Thr Gln His Val Ser Pro Met Arg
      210           215           220

Gln Val Glu Pro Pro Ala Lys Lys Pro Ala Thr Pro Ala Glu Asp Asp
      225           230           235           240

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Glu Asp Asp Asp Ile Asp Leu Phe Gly Ser Asp Asn Glu Glu Glu Asp  
245 250 255  
Lys Glu Ala Ala Gln Leu Arg Glu Glu Arg Leu Arg Xaa Tyr Ala Glu  
260 265 270  
Lys Lys Ala Lys Lys Xaa Ala Leu Val Ala Lys Ser Ser Ile Leu Leu  
275 280 285  
Asp Phe Lys Pro Trp Gly  
290

<210> 596  
<211> 134  
<212> PRT  
<213> Homo sapiens

<400> 596  
Val Ser Arg Leu Gly Leu Leu Thr Pro Leu Gly Cys Ser Phe Gly Thr  
1 5 10 15  
Asp Glu Trp Leu Cys Pro Val Thr Ala Leu Ser Leu Pro Gly Gly Tyr  
20 25 30  
Val His Ser Arg Pro Leu Pro Arg Leu Arg Pro Met Arg Tyr Gly Asp  
35 40 45  
Thr Leu Ala Pro Arg Ser Trp Arg His Arg Pro Leu Pro Trp His Ser  
50 55 60  
Ser Phe Ala Gly Asp Pro Pro Leu Pro Lys Ala Leu Ser Pro Cys Ser  
65 70 75 80  
His Ser Arg Arg Thr Ala Ala Arg Ala Ser Gly Ser Leu Ala Thr Gly  
85 90 95  
Phe Glu Arg Leu His Ser Trp Gly Leu Glu Gly Gly Val Pro Lys Ala  
100 105 110  
Leu Ser Lys Ser Gln Ser Ser Ser His Gln Ser Leu Tyr Lys Val Leu  
115 120 125  
Gly Pro Glu Ala Leu Pro  
130

<210> 597



<211> 91  
<212> PRT  
<213> Homo sapiens

<400> 597

Glu Gly Pro Glu Gly Ala Asn Leu Phe Ile Tyr His Leu Pro Gln Glu  
1 5 10 15  
Phe Gly Asp Gln Asp Ile Leu Gln Met Phe Met Pro Phe Gly Asn Val  
20 25 30  
Ile Ser Ala Lys Val Phe Ile Asp Lys Gln Thr Asn Leu Ser Lys Cys  
35 40 45  
Phe Gly Phe Val Ser Tyr Asp Asn Pro Val Ser Ala Gln Ala Ala Ile  
50 55 60  
Gln Ala Met Asn Gly Phe Gln Ile Gly Met Lys Arg Leu Lys Val Gln  
65 70 75 80  
Leu Lys Arg Ser Lys Asn Asp Ser Lys Pro Tyr  
85 90

<210> 598  
<211> 68  
<212> PRT  
<213> Homo sapiens

<400> 598

Arg Pro Thr Arg Pro Glu Lys Val Gly Ser Gly Gly Ser Ser Val Gly  
1 5 10 15  
Ser Gly Asp Ala Ser Ser Ser Arg His His Arg Arg Arg Arg Phe  
20 25 30  
His Leu Pro Gln Gln Pro Leu Leu Gln Arg Glu Val Trp Cys Val Gly  
35 40 45  
Thr Thr Gly Asn Ala Asn Gln Ala Gln Ser Ser Thr Glu Gln Thr Leu  
50 55 60  
Leu Lys Pro Lys  
65

<210> 599  
<211> 119  
<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (58)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (88)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (98)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (99)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 599

Phe Gly Arg Asp Gln Val Tyr Leu Ser Tyr Asn Asn Val Ser Ser Leu  
1 5 10 15

Lys Met Leu Val Ala Lys Asp Asn Trp Val Leu Ser Ser Glu Ile Ser  
20 25 30

Gln Val Arg Leu Tyr Thr Leu Glu Asp Asp Lys Phe Leu Ser Phe His  
35 40 45

Met Glu Met Val Val His Val Asp Ala Xaa Gln Ala Phe Leu Leu Leu  
50 55 60

Ser Asp Leu Xaa Gln Arg Pro Glu Trp Asp Lys His Tyr Arg Ser Val  
65 70 75 80

Glu Leu Val Gln Gln Val Asp Xaa Gly Arg Arg His Leu Pro Arg His  
85 90 95

Gln Xaa Xaa Pro Arg Arg Ser His Lys Ala Pro Gly Leu Arg Asp Pro  
100 105 110

Gly Leu Glu Ala Glu Ala Leu  
115

<210> 600  
<211> 177  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (1)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (8)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (69)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (135)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 600  
Xaa Glu Arg Leu Arg Ala Gln Xaa Glu Lys Ser Arg Asp Ser Gln Pro  
1 5 10 15  
Arg Leu Pro Leu Arg Phe Pro Ser Trp Arg Gly Pro Trp Cys Gly Ile  
20 25 30  
Glu Ile Ala Gly Tyr Gly Ala Glu Val Phe Arg Gln Tyr Trp Asp Ile  
35 40 45  
Pro Asp Gly Thr Asp Cys His Arg Lys Ala Tyr Ser Thr Thr Ser Ile  
50 55 60  
Ala Ser Val Ala Xaa Leu Thr Ala Ala Ala Tyr Arg Val Thr Leu Asn  
65 70 75 80  
Pro Pro Gly Thr Phe Leu Glu Gly Val Ala Lys Val Gly Gln Tyr Thr  
85 90 95  
Phe Thr Ala Ala Ala Val Gly Ala Val Phe Gly Leu Thr Thr Cys Ile  
100 105 110  
Ser Ala His Val Arg Glu Lys Pro Asp Asp Pro Leu Asn Tyr Phe Leu

115                      120                      125  
 Gly Gly Cys Ala Gly Gly Xaa Thr Leu Gly Ala Arg Thr His Asn Tyr  
     130                      135                      140  
 Gly Ile Gly Ala Ala Ala Cys Val Tyr Phe Gly Ile Ala Ala Ser Leu  
 145                      150                      155                      160  
 Val Lys Met Gly Arg Leu Glu Gly Trp Glu Val Phe Ala Lys Pro Lys  
                     165                      170                      175  
 Val

<210> 601  
 <211> 218  
 <212> PRT  
 <213> Homo sapiens

<400> 601  
 Arg Gly Gly Gly Gly Ala Ser Ser Cys Cys Cys Ala Pro Ser  
     1                      5                      10                      15  
 Pro Arg Gly Arg Pro Val Pro Ala Arg Thr Pro Arg Arg Cys Pro Arg  
                     20                      25                      30  
 Pro Ser Pro Gly Pro Ala Met Gly Leu Thr Val Ser Ala Leu Phe Ser  
                     35                      40                      45  
 Arg Ile Phe Gly Lys Lys Gln Met Arg Ile Leu Met Val Gly Leu Asp  
     50                      55                      60  
 Ala Ala Gly Lys Thr Thr Ile Leu Tyr Lys Leu Lys Leu Gly Glu Ile  
     65                      70                      75                      80  
 Val Thr Thr Ile Pro Thr Ile Gly Phe Asn Val Glu Thr Val Glu Tyr  
                     85                      90                      95  
 Lys Asn Ile Cys Phe Thr Val Trp Asp Val Gly Gly Gln Asp Lys Ile  
                     100                      105                      110  
 Arg Pro Leu Trp Arg His Tyr Phe Gln Asn Thr Gln Gly Leu Ile Phe  
                     115                      120                      125  
 Val Val Asp Ser Asn Asp Arg Glu Arg Val Gln Glu Ser Ala Asp Glu  
     130                      135                      140  
 Leu Gln Lys Met Leu Gln Glu Asp Glu Leu Arg Asp Ala Val Leu Leu  
 145                      150                      155                      160

Val Phe Ala Asn Lys Gln Asp Met Pro Asn Ala Met Pro Val Ser Glu  
 165 170 175

Leu Thr Asp Lys Leu Gly Leu Gln His Leu Arg Ser Arg Thr Trp Tyr  
 180 185 190

Val Gln Ala Thr Cys Ala Thr Gln Gly Thr Gly Leu Tyr Asp Gly Leu  
 195 200 205

Asp Trp Leu Ser His Glu Leu Ser Lys Arg  
 210 215

<210> 602

<211> 829

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (32)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (454)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 602

Pro Gly Gln Ala Gly Ala Glu Gly His Val Arg Cys Cys Pro Gly Glu  
 1 5 10 15

Glu Gln Lys Ala Gly Gly Glu Arg Arg Cys Pro Gly Pro Gln Arg Xaa  
 20 25 30

Gly Ala Ala Leu Gly Pro Gly Pro Gly Glu Ala Arg Leu Asp Tyr Ser  
 35 40 45

Glu Phe Phe Thr Glu Asp Val Gly Gln Leu Pro Gly Leu Thr Ile Trp  
 50 55 60

Gln Ile Glu Asn Phe Val Pro Val Leu Val Glu Glu Ala Phe His Gly  
 65 70 75 80

Lys Phe Tyr Glu Ala Asp Cys Tyr Ile Val Leu Lys Thr Phe Leu Asp  
 85 90 95

Asp Ser Gly Ser Leu Asn Trp Glu Ile Tyr Tyr Trp Ile Gly Gly Glu  
 100 105 110

Ala Thr Leu Asp Lys Lys Ala Cys Ser Ala Ile His Ala Val Asn Leu  
 115 120 125  
 Arg Asn Tyr Leu Gly Ala Glu Cys Arg Thr Val Arg Glu Glu Met Gly  
 130 135 140  
 Asp Glu Ser Glu Glu Phe Leu Gln Val Phe Asp Asn Asp Ile Ser Tyr  
 145 150 155 160  
 Ile Glu Gly Gly Thr Ala Ser Gly Phe Tyr Thr Val Glu Asp Thr His  
 165 170 175  
 Tyr Val Thr Arg Met Tyr Arg Val Tyr Gly Lys Lys Asn Ile Lys Leu  
 180 185 190  
 Glu Pro Val Pro Leu Lys Gly Thr Ser Leu Asp Pro Arg Phe Val Phe  
 195 200 205  
 Leu Leu Asp Arg Gly Leu Asp Ile Tyr Val Trp Arg Gly Ala Gln Ala  
 210 215 220  
 Thr Leu Ser Ser Thr Thr Lys Ala Arg Leu Phe Ala Glu Lys Ile Asn  
 225 230 235 240  
 Lys Asn Glu Arg Lys Gly Lys Ala Glu Ile Thr Leu Leu Val Gln Gly  
 245 250 255  
 Gln Glu Leu Pro Glu Phe Trp Glu Ala Leu Gly Gly Glu Pro Ser Glu  
 260 265 270  
 Ile Lys Lys His Val Pro Glu Asp Phe Trp Pro Pro Gln Pro Lys Leu  
 275 280 285  
 Tyr Lys Val Gly Leu Gly Leu Gly Tyr Leu Glu Leu Pro Gln Ile Asn  
 290 295 300  
 Tyr Lys Leu Ser Val Glu His Lys Gln Arg Pro Lys Val Glu Leu Met  
 305 310 315 320  
 Pro Arg Met Arg Leu Leu Gln Ser Leu Leu Asp Thr Arg Cys Val Asn  
 325 330 335  
 Ile Leu Asp Cys Trp Ser Asp Val Phe Ile Trp Leu Gly Arg Lys Ser  
 340 345 350  
 Pro Arg Leu Val Arg Ala Ala Ala Leu Lys Leu Gly Gln Glu Leu Cys  
 355 360 365  
 Gly Met Leu His Arg Pro Arg His Ala Thr Val Ser Arg Ser Leu Glu  
 370 375 380

Gly Thr Glu Ala Gln Val Phe Lys Ala Lys Phe Lys Asn Trp Asp Asp  
 385 390 395 400  
 Val Leu Thr Val Asp Tyr Thr Arg Asn Ala Glu Ala Val Leu Gln Ser  
 405 410 415  
 Pro Gly Leu Ser Gly Lys Val Lys Arg Asp Ala Glu Lys Lys Asp Gln  
 420 425 430  
 Met Lys Ala Asp Leu Thr Ala Leu Phe Leu Pro Arg Gln Pro Pro Met  
 435 440 445  
 Ser Leu Ala Glu Ala Xaa Gln Leu Met Glu Glu Trp Asn Glu Asp Leu  
 450 455 460  
 Asp Gly Met Glu Gly Phe Val Leu Glu Gly Lys Lys Phe Ala Arg Leu  
 465 470 475 480  
 Pro Glu Glu Glu Phe Gly His Phe Tyr Thr Gln Asp Cys Tyr Val Phe  
 485 490 495  
 Leu Cys Arg Tyr Trp Val Pro Val Glu Tyr Glu :Glu Glu Glu Lys Lys  
 500 505 510  
 Glu Asp Lys Glu Glu Lys Ala Glu Gly Lys Glu Gly Glu Glu Ala Thr  
 515 520 525  
 Ala Glu Ala Glu Glu Lys Gln Pro Glu Glu Asp Phe Gln Cys Ile Val  
 530 535 540  
 Tyr Phe Trp Gln Gly Arg Glu Ala Ser Asn Met Gly Trp Leu Thr Phe  
 545 550 555 560  
 Thr Phe Ser Leu Gln Lys Lys Phe Glu Ser Leu Phe Pro Gly Lys Leu  
 565 570 575  
 Glu Val Val Arg Met Thr Gln Gln Gln Glu Asn Pro Lys Phe Leu Ser  
 580 585 590  
 His Phe Lys Arg Lys Phe Ile Ile His Arg Gly Lys Arg Lys Ala Val  
 595 600 605  
 Gln Gly Ala Gln Gln Pro Ser Leu Tyr Gln Ile Arg Thr Asn Gly Ser  
 610 615 620  
 Ala Leu Cys Thr Arg Cys Ile Gln Ile Asn Thr Asp Ser Ser Leu Leu  
 625 630 635 640  
 Asn Ser Glu Phe Cys Phe Ile Leu Lys Val Pro Phe Glu Ser Glu Asp  
 645 650 655

Asn Gln Gly Ile Val Tyr Ala Trp Val Gly Arg Ala Ser Asp Pro Asp  
 660 665 670  
 Glu Ala Lys Leu Ala Glu Asp Ile Leu Asn Thr Met Phe Asp Thr Ser  
 675 680 685  
 Tyr Ser Lys Gln Val Ile Asn Glu Gly Glu Glu Pro Glu Asn Phe Phe  
 690 695 700  
 Trp Val Gly Ile Gly Ala Gln Lys Pro Tyr Asp Asp Asp Ala Glu Tyr  
 705 710 715 720  
 Met Lys His Thr Arg Leu Phe Arg Cys Ser Asn Glu Lys Gly Tyr Phe  
 725 730 735  
 Ala Val Thr Glu Lys Cys Ser Asp Phe Cys Gln Asp Asp Leu Ala Asp  
 740 745 750  
 Asp Asp Ile Met Leu Leu Asp Asn Gly Gln Glu Val Tyr Met Trp Val  
 755 760 765  
 Gly Thr Gln Thr Ser Gln Val Glu Ile Lys Leu Ser Leu Lys Ala Cys  
 770 775 780  
 Gln Val Tyr Ile Gln His Met Arg Ser Lys Glu His Glu Arg Pro Arg  
 785 790 795 800  
 Arg Leu Arg Leu Val Arg Lys Gly Asn Glu Gln His Ala Phe Thr Arg  
 805 810 815  
 Cys Phe His Ala Trp Ser Ala Phe Cys Lys Ala Leu Ala  
 820 825

<210> 603  
 <211> 221  
 <212> PRT  
 <213> Homo sapiens

<400> 603  
 Thr Glu Pro Pro Leu Ser Cys Cys Leu Pro Ala Thr Tyr Pro Ala Asp  
 1 5 10 15  
 Met Gly Thr Ala Gly Ala Met Gln Leu Cys Trp Val Ile Leu Gly Phe  
 20 25 30  
 Leu Leu Phe Arg Gly His Asn Ser Gln Pro Thr Met Thr Gln Thr Ser  
 35 40 45



Ser Ser Gln Gly Gly Leu Gly Gly Leu Ser Leu Thr Thr Glu Pro Val  
 50 55 60  
 Ser Ser Asn Pro Gly Tyr Ile Pro Ser Ser Glu Ala Asn Arg Pro Ser  
 65 70 75 80  
 His Leu Ser Ser Thr Gly Thr Pro Gly Ala Gly Val Pro Ser Ser Gly  
 85 90 95  
 Arg Asp Gly Gly Thr Ser Arg Asp Thr Phe Gln Thr Val Pro Pro Asn  
 100 105 110  
 Ser Thr Thr Met Ser Leu Ser Met Arg Glu Asp Ala Thr Ile Leu Pro  
 115 120 125  
 Ser Pro Thr Ser Glu Thr Val Leu Thr Val Ala Ala Phe Gly Val Ile  
 130 135 140  
 Ser Phe Ile Val Ile Leu Val Val Val Val Ile Ile Leu Val Gly Val  
 145 150 155 160  
 Val Ser Leu Arg Phe Lys Cys Arg Lys Ser Lys Glu Ser Glu Asp Pro  
 165 170 175  
 Gln Lys Pro Gly Ser Ser Gly Leu Ser Glu Ser Cys Ser Thr Ala Asn  
 180 185 190  
 Gly Glu Lys Asp Ser Ile Thr Leu Ile Ser Met Lys Asn Ile Asn Met  
 195 200 205  
 Asn Asn Gly Lys Gln Ser Leu Ser Ala Glu Lys Val Leu  
 210 215 220

&lt;210&gt; 604

&lt;211&gt; 97

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 604

Ser Cys Gly Leu Ser Leu Ile Lys Met Thr Thr Ser Gln Lys His Arg  
 1 5 10 15  
 Asp Phe Val Ala Glu Pro Met Gly Glu Lys Pro Val Gly Ser Leu Ala  
 20 25 30  
 Gly Ile Gly Glu Val Leu Gly Lys Lys Leu Glu Glu Arg Gly Phe Asp  
 35 40 45  
 Lys Ala Tyr Val Val Leu Gly Gln Phe Leu Val Leu Lys Lys Asp Glu

564

50                      55                      60  
 Asp Leu Phe Arg Glu Trp Leu Lys Asp Thr Cys Gly Ala Asn Ala Lys  
 65                      70                      75                      80  
 Gln Ser Arg Asp Cys Phe Gly Cys Leu Arg Glu Trp Cys Asp Ala Phe  
                          85                      90                      95  
 Leu

&lt;210&gt; 605

&lt;211&gt; 266

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (84)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 605

Gly Pro Arg Arg Leu Gly Ala Leu His Ala Ala Ala Thr Gly Ala Arg  
 1                      5                      10                      15  
 Cys Leu Val Glu Leu Leu Val Ala His Gly Ala Asp Leu Asn Ala Lys  
                          20                      25                      30  
 Ser Leu Met Asp Glu Thr Pro Leu Asp Val Cys Gly Asp Glu Glu Val  
                          35                      40                      45  
 Arg Ala Lys Leu Leu Glu Leu Lys His Lys His Asp Ala Leu Leu Arg  
                          50                      55                      60  
 Ala Gln Ser Arg Gln Arg Ser Leu Leu Arg Arg Arg Thr Ser Ser Ala  
 65                      70                      75                      80  
 Gly Ser Arg Xaa Lys Val Val Arg Arg Val Ser Leu Thr Gln Arg Thr  
                          85                      90                      95  
 Asp Leu Tyr Arg Lys Gln His Ala Gln Glu Ala Ile Val Trp Gln Gln  
                          100                      105                      110  
 Pro Pro Pro Thr Ser Pro Glu Pro Pro Glu Asp Asn Asp Asp Arg Gln  
                          115                      120                      125  
 Thr Gly Ala Glu Leu Arg Pro Pro Pro Pro Glu Glu Asp Asn Pro Glu  
 130                      135                      140

Val Val Arg Pro His Asn Gly Arg Val Gly Gly Ser Pro Val Arg His  
145 150 155 160

Leu Tyr Ser Lys Arg Leu Asp Arg Ser Val Ser Tyr Gln Leu Ser Pro  
165 170 175

Leu Asp Ser Thr Thr Pro His Thr Leu Val His Asp Lys Ala His His  
180 185 190

Thr Leu Ala Asp Leu Lys Arg Gln Arg Ala Ala Ala Lys Leu Gln Arg  
195 200 205

Pro Pro Pro Glu Gly Pro Glu Ser Pro Glu Thr Ala Glu Pro Gly Leu  
210 215 220

Pro Gly Asp Thr Val Thr Pro Gln Pro Asp Cys Gly Phe Arg Ala Gly  
225 230 235 240

Gly Asp Pro Pro Leu Leu Lys Leu Thr Ala Pro Ala Val Glu Ala Pro  
245 250 255

Val Glu Arg Arg Pro Cys Cys Leu Leu Met  
260 265

<210> 606

<211> 331

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (91)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (285)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 606

His Asp Ser Cys Phe Val Glu Met Gln Ala Gln Lys Val Met His Val  
1 5 10 15

Ser Ser Ala Glu Leu Asn Tyr Ser Leu Pro Tyr Asp Ser Lys His Gln  
20 25 30

Ile Arg Asn Ala Ser Asn Val Lys His His Asp Ser Ser Ala Leu Gly  
35 40 45

Val Tyr Ser Tyr Ile Pro Leu Val Glu Asn Pro Tyr Phe Ser Ser Trp  
 50 55 60  
 Pro Pro Ser Gly Thr Ser Ser Lys Met Ser Leu Asp Leu Pro Glu Lys  
 65 70 75 80  
 Gln Asp Gly Thr Val Phe Pro Ser Ser Leu Xaa Pro Thr Ser Ser Thr  
 85 90 95  
 Ser Leu Phe Ser Tyr Tyr Asn Ser His Asp Ser Leu Ser Leu Asn Ser  
 100 105 110  
 Pro Thr Asn Ile Ser Ser Leu Leu Asn Gln Glu Ser Ala Val Leu Ala  
 115 120 125  
 Thr Ala Pro Arg Ile Asp Asp Glu Ile Pro Pro Pro Leu Pro Val Arg  
 130 135 140  
 Thr Pro Glu Ser Phe Ile Val Val Glu Glu Ala Gly Glu Phe Ser Pro  
 145 150 155 160  
 Asn Val Pro Lys Ser Leu Ser Ser Ala Val Lys Val Lys Ile Gly Thr  
 165 170 175  
 Ser Leu Glu Trp Gly Gly Thr Ser Glu Pro Lys Lys Phe Asp Asp Ser  
 180 185 190  
 Val Ile Leu Arg Pro Ser Lys Ser Val Lys Leu Arg Ser Pro Lys Ser  
 195 200 205  
 Glu Leu His Gln Asp Arg Ser Ser Pro Pro Pro Pro Leu Pro Glu Arg  
 210 215 220  
 Thr Leu Glu Ser Phe Phe Leu Ala Asp Glu Asp Cys Met Gln Ala Gln  
 225 230 235 240  
 Ser Ile Glu Thr Tyr Ser Thr Ser Tyr Pro Asp Thr Met Glu Asn Ser  
 245 250 255  
 Thr Ser Ser Lys Gln Thr Leu Lys Thr Pro Gly Lys Ser Phe Thr Arg  
 260 265 270  
 Ser Lys Ser Leu Lys Ile Leu Arg Asn Met Lys Lys Xaa Ile Cys Asn  
 275 280 285  
 Ser Cys Pro Pro Asn Lys Pro Ala Glu Ser Val Gln Ser Asn Asn Ser  
 290 295 300  
 Ser Ser Phe Leu Asn Phe Gly Phe Ala Asn Arg Phe Ser Lys Pro Lys  
 305 310 315 320

Gly Pro Arg Asn Pro Pro Pro Thr Trp Asn Ile  
 325 330

<210> 607

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 607

Ala Ala Pro Ser Glu Pro Lys Ala Arg Gly Gly His Gly Gly Ala Leu  
 1 5 10 15

Ala Arg Leu Glu Thr Met Pro Lys Leu Gln Gly Phe Glu Phe Trp Ser  
 20 25 30

Arg Thr Leu Arg Gly Ala Arg His Val Val Ala Pro Met Val Asp Gln  
 35 40 45

Ser Glu Leu Ala Trp Arg Leu Leu Ser Arg Arg His Gly Ala Gln Leu  
 50 55 60

Cys Tyr Thr Pro Met Leu His Ala Gln Val Phe Val Arg Xaa Ala Asn  
 65 70 75 80

Tyr Arg Lys Glu Asn Leu Tyr Cys Glu Val Cys Pro Glu Asp Arg Pro  
 85 90 95

Leu Ile Val Gln Phe Cys Ala Asn Asp Pro Glu Val Phe Val Gln Ala  
 100 105 110

Ala Leu Leu Ala Gln Asp Tyr Cys Asp Ala Ile Asp Leu Asn Leu Gly  
 115 120 125

Cys Pro Gln Met Ile Ala Lys Arg Gly His Tyr Gly Ala Phe Leu Gln  
 130 135 140

Asp Glu Trp Asp Leu Leu Gln Arg Met Ile Leu Leu Ala His Glu Lys  
 145 150 155 160

Leu Ser Val Pro Val Thr Cys Lys Ile Arg Val Phe Pro Glu Ile Asp  
 165 170 175

Lys Thr Val Ser Thr Pro Arg Cys Trp Arg Arg Pro Ala Ala Ser Cys  
 180 185 190

&lt;210&gt; 608

&lt;211&gt; 415

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 608

His Ile Lys Cys Pro His Ser Lys Tyr Gly Cys Thr Phe Ile Gly Asn  
 1 5 10 15

Gln Asp Thr Tyr Glu Thr His Leu Glu Thr Cys Arg Phe Glu Gly Leu  
 20 25 30

Lys Glu Phe Leu Gln Gln Thr Asp Asp Arg Phe His Glu Met His Val  
 35 40 45

Ala Leu Ala Gln Lys Asp Gln Glu Ile Ala Phe Leu Arg Ser Met Leu  
 50 55 60

Gly Lys Leu Ser Glu Lys Ile Asp Gln Leu Glu Lys Ser Leu Glu Leu  
 65 70 75 80

Lys Phe Asp Val Leu Asp Glu Asn Gln Ser Lys Leu Ser Glu Asp Leu  
 85 90 95

Met Glu Phe Arg Arg Asp Ala Ser Met Leu Asn Asp Glu Leu Ser His  
 100 105 110

Ile Asn Ala Arg Leu Asn Met Gly Ile Leu Gly Ser Tyr Asp Pro Gln  
 115 120 125

Gln Ile Phe Lys Cys Lys Gly Thr Phe Val Gly His Gln Gly Pro Val  
 130 135 140

Trp Cys Leu Cys Val Tyr Ser Met Gly Asp Leu Leu Phe Ser Gly Ser  
 145 150 155 160

Ser Asp Lys Thr Ile Lys Val Trp Asp Thr Cys Thr Thr Tyr Lys Cys  
 165 170 175

Gln Lys Thr Leu Glu Gly His Asp Gly Ile Val Leu Ala Leu Cys Ile  
 180 185 190

Gln Gly Cys Lys Leu Tyr Ser Gly Ser Ala Asp Cys Thr Ile Ile Val  
 195 200 205

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Trp Asp Ile Gln Asn Leu Gln Lys Val Asn Thr Ile Arg Ala His Asp
 210                      215                      220

Asn Pro Val Cys Thr Leu Val Ser Ser His Asn Val Leu Phe Ser Gly
225                      230                      235                      240

Ser Leu Lys Ala Ile Lys Val Trp Asp Ile Val Gly Thr Glu Leu Lys
                      245                      250                      255

Leu Lys Lys Glu Leu Thr Gly Leu Asn His Trp Val Arg Ala Leu Val
                      260                      265                      270

Ala Ala Gln Ser Tyr Leu Tyr Ser Gly Ser Tyr Gln Thr Ile Lys Ile
                      275                      280                      285

Trp Asp Ile Arg Thr Leu Asp Cys Ile His Val Leu Gln Thr Ser Gly
 290                      295                      300

Gly Ser Val Tyr Ser Ile Ala Val Thr Asn His His Ile Val Cys Gly
305                      310                      315                      320

Thr Tyr Glu Asn Leu Ile His Val Trp Asp Ile Glu Ser Lys Glu Gln
                      325                      330                      335

Val Arg Thr Leu Thr Gly His Val Gly Thr Val Tyr Ala Leu Ala Val
                      340                      345                      350

Ile Ser Thr Pro Asp Gln Thr Lys Val Phe Ser Ala Ser Tyr Asp Arg
                      355                      360                      365

Ser Leu Arg Val Trp Ser Met Asp Asn Met Ile Cys Thr Gln Thr Leu
                      370                      375                      380

Leu Arg His Gln Gly Ser Val Thr Ala Leu Ala Val Ser Arg Gly Arg
385                      390                      395                      400

Leu Phe Ser Gly Ala Val Asp Ser Thr Val Lys Val Trp Thr Cys
                      405                      410                      415

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&lt;210&gt; 609

&lt;211&gt; 48

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 609

Phe	Ser	Glu	Leu	Asn	Gln	Cys	Phe	Tyr	Ile	Cys	Phe	Phe	Phe	Tyr	Ala
1				5					10					15	

Ser	Trp	Lys	Trp	Arg	Met	Lys	Ile	Gln	Leu	Xaa	Cys	Ser	Asn	Ser	Arg
			20					25					30		

Arg	Xaa	Val	Ser	Thr	Glu	Lys	Gly	Thr	Cys	Phe	Phe	Thr	Pro	Glu	Leu
		35					40						45		

&lt;210&gt; 610

&lt;211&gt; 241

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (13)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (37)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 610



571

Xaa Asp Xaa Gly Arg Pro Xaa Arg Thr Ala Glu Ser Xaa Phe Gly Ile  
1 5 10 15  
Asn Leu Lys Gly Pro Lys Ile Lys Gly Gly Ala Asp Val Ser Gly Gly  
20 25 30  
Val Ser Ala Pro Xaa Ile Ser Leu Gly Glu Gly His Leu Ser Val Lys  
35 40 45  
Gly Ser Gly Gly Glu Trp Lys Gly Pro Gln Val Ser Ser Ala Leu Asn  
50 55 60  
Leu Asp Thr Ser Lys Phe Ala Gly Gly Leu His Phe Ser Gly Pro Lys  
65 70 75 80  
Val Glu Gly Gly Val Lys Gly Gly Gln Ile Gly Leu Gln Ala Pro Gly  
85 90 95  
Leu Ser Val Ser Gly Pro Gln Gly His Leu Glu Ser Gly Ser Gly Lys  
100 105 110  
Val Thr Phe Pro Lys Met Lys Ile Pro Lys Phe Thr Phe Ser Gly Arg  
115 120 125  
Glu Leu Val Gly Arg Glu Met Gly Val Asp Val His Phe Pro Lys Ala  
130 135 140  
Glu Ala Ser Ile Gln Ala Gly Ala Gly Asp Gly Glu Trp Glu Glu Ser  
145 150 155 160  
Glu Val Lys Leu Lys Lys Ser Lys Ile Lys Met Pro Lys Phe Asn Phe  
165 170 175  
Ser Lys Pro Lys Gly Lys Gly Gly Val Thr Gly Ser Pro Glu Ala Ser  
180 185 190  
Ile Ser Gly Ser Lys Gly Asp Leu Lys Ser Ser Lys Ala Ser Leu Gly  
195 200 205  
Ser Leu Glu Gly Glu Ala Glu Ala Glu Ala Ser Ser Pro Lys Gly Lys  
210 215 220  
Phe Ser Leu Phe Lys Ser Lys Lys Pro Arg His Arg Cys Lys Phe Ile  
225 230 235 240

Gln

&lt;210&gt; 611

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 611

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His Tyr Arg Arg Tyr Ala Cys Arg Tyr Arg Ser Gly Ile Pro Gly Ser
 1           5           10           15

Thr His Ala Ser Gly Val Ala Asp Gly Gly Gln Val Phe Leu Phe Pro
      20           25           30

Glu Thr Gly Ser Val Gln Thr Ala Asn Ala His Arg Trp Pro Arg Gly
      35           40           45

Gly Gly Ser Gln Gly Val Trp Val Phe Leu Gly Phe Phe Ser Val Val
 50           55           60

Ser Phe Thr Gln Gly Trp Trp Ser Gln Pro Val Trp Cys
 65           70           75

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&lt;210&gt; 612

&lt;211&gt; 137

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 612

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Leu Gln Val Pro Val Arg Asn Ser Gly Ser Pro Thr Arg Gln Ala Ala
 1           5           10           15

Ala Met Thr Phe Cys Arg Leu Leu Asn Arg Cys Gly Glu Ala Ala Arg
      20           25           30

Ser Leu Pro Leu Gly Ala Arg Cys Phe Gly Val Arg Val Ser Pro Thr
      35           40           45

Gly Glu Lys Val Thr His Thr Gly Gln Val Tyr Asp Asp Lys Asp Tyr
 50           55           60

Arg Arg Ile Arg Phe Val Gly Arg Gln Lys Glu Val Asn Glu Asn Phe
 65           70           75           80

Ala Ile Asp Leu Ile Ala Glu Gln Pro Val Ser Glu Val Glu Thr Arg
      85           90           95

Val Ile Ala Cys Asp Gly Gly Gly Gly Ala Leu Gly His Pro Lys Val
      100           105           110

Tyr Ile Asn Leu Asp Lys Glu Thr Lys Thr Gly Thr Cys Gly Tyr Cys
      115           120           125

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Gly Leu Gln Phe Arg Gln His His His  
130 135

<210> 613

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (75)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (85)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (98)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (111)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (116)

<223> Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 613

Tyr Ser Thr Asp Asn Asn Asn Asn Trp Tyr Ser Ile Phe Tyr Leu His  
 1 5 10 15  
 Ser Ser Phe Leu Gly Glu Asn Ala Glu Lys Leu Leu Gln Phe Lys Arg  
 20 25 30  
 Trp Phe Trp Ser Ile Val Glu Lys Met Ser Met Thr Glu Arg Gln Asp  
 35 40 45  
 Leu Xaa Tyr Phe Trp Thr Ser Ser Pro Ser Leu Pro Ala Ser Glu Glu  
 50 55 60  
 Gly Phe Gln Pro Met Pro Ser Ile Thr Ile Xaa Pro Pro Asp Asp Xaa  
 65 70 75 80  
 His Leu Pro Thr Xaa Lys Tyr Leu His Phe Leu Asp Phe Thr Phe Pro  
 85 90 95  
 Leu Xaa Ser Phe Lys Gln Asp Ser Xaa Asn Arg Lys Leu Val Xaa Ser  
 100 105 110  
 Pro Phe Arg Xaa Gln Lys Phe Trp Val Leu  
 115 120

&lt;210&gt; 614

&lt;211&gt; 62

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 614

Phe Phe Ile Gly Leu Glu Thr Arg Ala Asn Ser Ile Met Phe Ser Lys  
 1 5 10 15  
 Glu Thr Asp Leu Ser Cys Trp Ile Arg Gly Thr Asn Pro Thr Tyr Met  
 20 25 30  
 Ile Phe Phe Leu Phe Leu Ser Cys Ser Tyr Gly Thr Val Leu Phe Gly  
 35 40 45  
 Thr Phe Ala Thr Arg Asp Asn Thr Thr Phe Leu Thr Leu Ile  
 50 55 60

&lt;210&gt; 615

&lt;211&gt; 159

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

575

&lt;400&gt; 615

Val Gly Leu Pro Asn Met Ala Gln Ser Ile Asn Ile Thr Glu Leu Asn  
 1 5 10 15  
 Leu Pro Gln Leu Glu Met Leu Lys Asn Gln Leu Asp Gln Glu Val Glu  
 20 25 30  
 Phe Leu Ser Thr Ser Ile Ala Gln Leu Lys Val Val Gln Thr Lys Tyr  
 35 40 45  
 Val Glu Ala Lys Asp Cys Leu Asn Val Leu Asn Lys Ser Asn Glu Gly  
 50 55 60  
 Lys Glu Leu Leu Val Pro Leu Thr Ser Ser Met Tyr Val Pro Gly Lys  
 65 70 75 80  
 Leu His Asp Val Glu His Val Leu Ile Asp Val Gly Thr Gly Tyr Tyr  
 85 90 95  
 Val Glu Lys Thr Ala Glu Asp Ala Lys Asp Phe Phe Lys Arg Lys Ile  
 100 105 110  
 Asp Phe Leu Thr Lys Gln Met Glu Lys Ile Gln Pro Ala Leu Gln Glu  
 115 120 125  
 Lys His Ala Met Lys Gln Ala Val Met Glu Met Met Ser Gln Lys Ile  
 130 135 140  
 Gln Gln Leu Thr Ala Leu Gly Ala Ala Gln Ala Thr Ala Lys Ala  
 145 150 155

&lt;210&gt; 616

&lt;211&gt; 93

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; {8}

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 616

Lys Val Ala Cys Arg Tyr Arg Xaa Gly Ile Pro Gly Arg Pro Thr Arg  
 1 5 10 15  
 Pro Gly Thr Gln Asp Ala Glu Gly Lys Lys Ala Lys Gly Lys Lys Val  
 20 25 30

Ala Pro Ala Pro Ala Val Val Lys Lys Gln Glu Ala Lys Lys Val Val  
           35                  40                  45

Asn Pro Leu Phe Glu Lys Arg Pro Lys Asn Phe Gly Ile Gly Gln Asp  
       50                  55                  60

Ile Gln Pro Lys Arg Asp Leu Thr Arg Phe Val Lys Trp Pro Arg Tyr  
       65                  70                  75                  80

Ile Arg Leu Gln Arg His Ala Arg Ser Ser Thr Ser Gly  
                   85                  90

&lt;210&gt; 617

&lt;211&gt; 362

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (307)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 617

Ser Arg Val Asp Pro Arg Val Arg Arg Gly Val Pro Tyr Gln Leu Gly  
       1                  5                  10                  15

Pro His Gly His Arg Gln Gly Leu Glu Ala Pro Leu Tyr Leu Thr Pro  
           20                  25                  30

Glu Gly Trp Ser Leu Phe Leu Gln Arg Tyr Tyr Gln Val Val His Glu  
       35                  40                  45

Gly Ala Glu Leu Arg His Leu Asp Thr Gln Val Gln Arg Cys Glu Asp  
       50                  55                  60

Ile Leu Gln Gln Leu Gln Ala Val Val Pro Gln Ile Asp Met Glu Gly  
       65                  70                  75                  80

Asp Arg Asn Ile Trp Ile Val Lys Pro Gly Ala Lys Ser Arg Gly Arg  
           85                  90                  95

Gly Ile Met Cys Met Asp His Leu Glu Glu Met Leu Lys Leu Val Asn  
           100                  105                  110

Gly Asn Pro Val Val Met Lys Asp Gly Lys Trp Val Val Gln Lys Tyr  
       115                  120                  125

Ile Glu Arg Pro Leu Leu Ile Phe Gly Thr Lys Phe Asp Leu Arg Gln  
       130                  135                  140

Trp Phe Leu Val Thr Asp Trp Asn Pro Leu Thr Val Trp Phe Tyr Arg  
 145 150 155 160  
 Asp Ser Tyr Ile Arg Phe Ser Thr Gln Pro Phe Ser Leu Lys Asn Leu  
 165 170 175  
 Asp Asn Ser Val His Leu Cys Asn Asn Ser Ile Gln Lys His Leu Glu  
 180 185 190  
 Asn Ser Cys His Arg His Pro Leu Leu Pro Pro Asp Asn Met Trp Ser  
 195 200 205  
 Ser Gln Arg Phe Gln Ala His Leu Gln Glu Met Gly Ala Pro Asn Ala  
 210 215 220  
 Trp Ser Thr Ile Ile Val Pro Gly Met Lys Asp Ala Val Ile His Ala  
 225 230 235 240  
 Leu Gln Thr Ser Gln Asp Thr Val Gln Cys Arg Lys Ala Ser Phe Glu  
 245 250 255  
 Leu Tyr Gly Ala Asp Phe Val Phe Gly Glu Asp Phe Gln Pro Trp Leu  
 260 265 270  
 Ile Glu Ile Asn Ala Ser Pro Thr Met Ala Pro Ser Thr Ala Val Thr  
 275 280 285  
 Ala Arg Leu Cys Ala Gly Val Gln Ala Asp Thr Leu Arg Val Val Ile  
 290 295 300  
 Asp Arg Xaa Leu Asp Arg Asn Cys Asp Thr Gly Ala Phe Glu Leu Ile  
 305 310 315 320  
 Tyr Lys Gln Pro Ala Val Glu Val Pro Gln Tyr Val Gly Ile Arg Leu  
 325 330 335  
 Leu Val Glu Gly Phe Thr Ile Lys Lys Pro Met Ala Met Cys His Arg  
 340 345 350  
 Arg Met Gly Val Arg Gln Gln Ser Leu Cys  
 355 360

&lt;210&gt; 618

&lt;211&gt; 328

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 618

Ile Arg Met Arg Glu Trp Trp Val Gln Val Gly Leu Leu Ala Val Pro  
 1 5 10 15  
 Leu Leu Ala Ala Tyr Leu His Ile Pro Pro Pro Gln Leu Ser Pro Ala  
 20 25 30  
 Leu His Ser Trp Lys Ser Ser Gly Lys Phe Phe Thr Tyr Lys Gly Leu  
 35 40 45  
 Arg Ile Phe Tyr Gln Asp Ser Val Gly Val Val Gly Ser Pro Glu Ile  
 50 55 60  
 Val Val Leu Leu His Gly Phe Pro Thr Ser Ser Tyr Asp Trp Tyr Lys  
 65 70 75 80  
 Ile Trp Glu Gly Leu Thr Leu Arg Phe His Arg Val Ile Ala Leu Asp  
 85 90 95  
 Phe Leu Gly Phe Gly Phe Ser Asp Lys Pro Arg Pro His His Tyr Ser  
 100 105 110  
 Ile Phe Glu Gln Ala Ser Ile Val Glu Ala Leu Leu Arg His Leu Gly  
 115 120 125  
 Leu Gln Asn Arg Arg Ile Asn Leu Leu Ser His Asp Tyr Gly Asp Ile  
 130 135 140  
 Val Ala Gln Glu Leu Leu Tyr Arg Tyr Lys Gln Asn Arg Ser Gly Arg  
 145 150 155 160  
 Leu Thr Ile Lys Ser Leu Cys Leu Ser Asn Gly Gly Ile Phe Pro Glu  
 165 170 175  
 Thr His Arg Pro Leu Leu Leu Gln Lys Leu Leu Lys Asp Gly Gly Val  
 180 185 190  
 Leu Ser Pro Ile Leu Thr Arg Leu Met Asn Phe Phe Val Phe Ser Arg  
 195 200 205  
 Gly Leu Thr Pro Val Phe Gly Pro Tyr Thr Arg Pro Ser Glu Ser Glu  
 210 215 220  
 Leu Trp Asp Met Trp Ala Gly Ile Arg Asn Asn Asp Gly Asn Leu Val  
 225 230 235 240  
 Ile Asp Ser Leu Leu Gln Tyr Ile Asn Gln Arg Lys Lys Phe Arg Arg  
 245 250 255  
 Arg Trp Val Gly Ala Leu Ala Ser Val Thr Ile Pro Ile His Phe Ile  
 260 265 270



Tyr Gly Pro Leu Asp Pro Val Asn Pro Tyr Pro Glu Phe Leu Glu Leu  
 275 280 285

Tyr Arg Lys Thr Leu Pro Arg Ser Thr Val Ser Ile Leu Asp Asp His  
 290 295 300

Ile Ser His Tyr Pro Gln Leu Glu Asp Pro Met Gly Phe Leu Asn Ala  
 305 310 315 320

Tyr Met Gly Phe Ile Asn Ser Phe  
 325

<210> 619

<211> 271

<212> PRT

<213> Homo sapiens

<400> 619

Asn Met Asp Pro Pro Gly Leu Gln Gly Val Gln Gly Thr Val Ala Ala  
 1 5 10 15

Cys Gly Ala Cys Tyr Trp Leu Leu Gly Leu Met Ala Val Arg Ala Ser  
 20 25 30

Phe Glu Asn Asn Cys Glu Ile Gly Cys Phe Ala Lys Leu Thr Asn Thr  
 35 40 45

Tyr Cys Leu Val Ala Ile Gly Gly Ser Glu Asn Phe Tyr Ser Val Phe  
 50 55 60

Glu Gly Glu Leu Ser Asp Thr Ile Pro Val Val His Ala Ser Ile Ala  
 65 70 75 80

Gly Cys Arg Ile Ile Gly Arg Met Cys Val Gly Asn Arg His Gly Leu  
 85 90 95

Leu Val Pro Asn Asn Thr Thr Asp Gln Glu Leu Gln His Ile Arg Asn  
 100 105 110

Ser Leu Pro Asp Thr Val Gln Ile Arg Arg Val Glu Glu Arg Leu Ser  
 115 120 125

Ala Leu Gly Asn Val Thr Thr Cys Asn Asp Tyr Val Ala Leu Val His  
 130 135 140

Pro Asp Leu Asp Arg Glu Thr Glu Glu Ile Leu Ala Asp Val Leu Lys  
 145 150 155 160

Val Glu Val Phe Arg Gln Thr Val Ala Asp Gln Val Leu Val Gly Ser

580

	165		170		175
Tyr Cys Val Phe Ser Asn Gln Gly Gly Leu Val His Pro Lys Thr Ser					
180		185		190	
Ile Glu Asp Gln Asp Glu Leu Ser Ser Leu Leu Gln Val Pro Leu Val					
195		200		205	
Ala Gly Thr Val Asn Arg Gly Ser Glu Val Ile Ala Ala Gly Met Val					
210		215		220	
Val Asn Asp Trp Cys Ala Phe Cys Gly Leu Asp Thr Thr Ser Thr Glu					
225		230		235	240
Leu Ser Val Val Glu Ser Val Phe Lys Leu Asn Glu Ala Gln Pro Ser					
	245		250		255
Thr Ile Ala Thr Ser Met Arg Asp Ser Leu Ile Asp Ser Leu Thr					
	260		265		270

&lt;210&gt; 620

&lt;211&gt; 88

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 620

Gly Ser Ala Ala Met Lys Val Lys Ile Lys Cys Trp Asn Gly Val Ala					
1		5		10	15
Thr Trp Leu Trp Val Ala Asn Asp Glu Asn Cys Gly Ile Cys Arg Met					
	20		25		30
Ala Phe Asn Gly Cys Cys Pro Asp Cys Lys Val Pro Gly Asp Asp Cys					
	35		40		45
Pro Leu Val Trp Gly Gln Cys Ser His Cys Phe His Met His Cys Ile					
	50		55		60
Leu Lys Trp Leu His Ala Gln Gln Val Gln Gln His Cys Pro Met Cys					
65		70		75	80
Arg Gln Glu Trp Lys Phe Lys Glu					
	85				

&lt;210&gt; 621

&lt;211&gt; 46

&lt;212&gt; PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 621

Ala Gly Thr Ser Arg Ser Glu Gly Lys Arg Ser Ser Val Leu Thr Arg  
1 5 10 15

Thr Glu Phe Gln Ile Glu Met Phe Gln Thr Ile Glu Gly Glu Lys Trp  
20 25 30

Pro Gly Xaa Ser Ile Asn Leu Ser Xaa Phe His Gly Cys Phe  
35 40 45

<210> 622

<211> 103

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 622

Gly Arg Pro Thr Arg Pro Arg Gly Arg Gly Arg Ser Ser Ala Cys Leu  
1 5 10 15

Leu Leu Glu Gly Asp Gly Pro Ala Arg Leu Trp Ala Pro Thr Ser Pro  
20 25 30

Gly Val Xaa Xaa Glu Arg Phe Ala Glu Glu Arg Gly Ser Gly Arg Ala  
35 40 45

Leu Asn Ala Gly Pro Lys His Pro Gly Ser Leu His Ser Pro Arg Pro  
50 55 60

Gln Thr Leu Thr Lys Thr Trp Ile Cys Ser Arg Phe Ser Cys Ser Arg  
 65 70 75 80

Ser Ser Arg Ser Cys Pro Arg Leu Leu Arg Leu Arg Ala Glu Lys Lys  
 85 90 95

Val Cys Gln Ala Trp Thr Gln  
 100

<210> 623

<211> 103

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (60)

<223> Xaa equals any of the naturally occurring-L-amino acids

<400> 623

Gly Arg Pro Thr Arg Pro Thr Ser Ser Arg Ser Arg Ala Ala Arg Pro  
 1 5 10 15

Phe Phe Phe Phe Phe Phe Phe Trp Phe Pro Glu Phe Gly Phe Ile Leu  
 20 25 30

Gln Tyr Arg Asn His Leu Glu Pro Ser Glu Thr Asp Ile Pro Glu Ala  
 35 40 45

Glu Ala Leu Ser Asn Gln Tyr Cys Val Ala Leu Xaa Pro Leu Arg Lys  
 50 55 60

Pro His Leu Gly Tyr Lys Arg Ser Phe Tyr Val Tyr Pro Leu Tyr His  
 65 70 75 80

Gly Phe Leu Ser Pro Leu Leu Leu Pro Ile Leu Pro Gly Glu Asn Thr  
 85 90 95

Ala Gln Arg Leu Pro Ser Glu  
 100

<210> 624

<211> 305

<212> PRT

<213> Homo sapiens

<220>  
 <221> SITE  
 <222> (116)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (117)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (219)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 624 .  
 Thr Gln Asp Leu Trp Met Ser Cys Pro Val Gln Thr Met Asp Pro Glu  
 1 5 10 15  
 Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Gly Leu Pro Gln Glu Gln  
 20 25 30  
 Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg Pro Leu Pro Gly  
 35 40 45  
 Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg Leu Lys Ala Gln  
 50 55 60  
 Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His Ser Ala Thr Leu  
 65 70 75 80  
 Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu Arg Leu Gly Leu  
 85 90 95  
 Thr Ser Tyr Arg Asp Phe Leu Gly Thr Asn Trp Ser Ser Ser Ala Ala  
 100 105 110  
 Trp Leu Arg Xaa Xaa Gly Ala Thr Asp Trp Gly Asp Thr Gln Ala Tyr  
 115 120 125  
 Leu Ala Asp Pro Leu Gly Val Gly Ala Ala Leu Ala Thr Ala Asp Asp  
 130 135 140  
 Phe Leu Val Phe Leu Arg Arg Ser Arg Gln Val Ala Glu Ala Pro Gly  
 145 150 155 160  
 Leu Val Asp Val Pro Gly Gly His Pro Glu Pro Gln Ala Leu Cys Pro  
 165 170 175  
 Gly Gly Ser Pro Gln His Gln Asp Leu Ala Gly Gln Leu Val Val His  
 180 185 190

Glu Leu Phe Ser Ser Val Leu Gln Glu Ile Cys Asp Glu Val Asn Leu  
 195 200 205  
 Pro Leu Leu Thr Leu Ser Gln Pro Leu Leu Xaa Gly Ile Ala Arg Asn  
 210 215 220  
 Glu Thr Ser Ala Gly Arg Ala Ser Ala Glu Phe Tyr Val Gln Cys Ser  
 225 230 235 240  
 Leu Thr Ser Glu Gln Val Arg Lys His Tyr Leu Ser Gly Gly Pro Glu  
 245 250 255  
 Ala His Glu Ser Thr Gly Ile Phe Phe Val Glu Thr Gln Asn Val Arg  
 260 265 270  
 Arg Leu Pro Glu Thr Glu Met Trp Ala Glu Leu Cys Pro Ser Pro Lys  
 275 280 285  
 Ala Pro Ser Ser Ser Thr Thr Gly Phe Arg Glu Val Pro Leu Glu Arg  
 290 295 300  
 Pro  
 305

<210> 625  
 <211> 102  
 <212> PRT  
 <213> Homo sapiens

<400> 625  
 Ser Ala Met Lys Ala Ser Gly Thr Leu Arg Glu Tyr Lys Val Val Gly  
 1 5 10 15  
 Arg Cys Leu Pro Thr Pro Lys Cys Arg Thr Pro Pro Leu Tyr Arg Met  
 20 25 30  
 Arg Ile Phe Ala Pro Asn His Val Val Ala Lys Ser Arg Phe Trp Tyr  
 35 40 45  
 Phe Val Ser Gln Leu Lys Lys Met Lys Lys Ser Ser Gly Glu Ile Val  
 50 55 60  
 Tyr Cys Gly Gln Val Phe Glu Lys Ser Pro Leu Arg Val Lys Asn Phe  
 65 70 75 80  
 Gly Ile Trp Leu Arg Tyr Asp Ser Arg Ser Gly Thr His Asn Met Tyr  
 85 90 95

Arg Gly Val Pro Gly Thr  
100

<210> 626

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 626

Ala Leu Trp Val Lys Ala Trp Arg Gln Glu Ser Glu Gly Gln Phe Gln  
1 5 10 15

Glu Thr Gln Phe Ile Asn Phe His Gln His Leu Pro Gly Pro Cys Leu  
20 25 30

Gly Thr Glu Xaa Pro Ser Pro Glu Ser Gly His His Phe Pro Phe Gln  
35 40 45

Ser Ile Glu Cys Arg Gly Ile Gln Gly Met Gly  
50 55

<210> 627

<211> 220

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (93)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 627

Arg Leu Val Val Thr Glu Glu Asp Gly Gly Ala Arg Pro Glu Ala Leu  
1 5 10 15

Gly Lys Ile Ala Pro Arg Thr Pro Ala Glu Leu Gly Ala Arg Ala Asp  
20 25 30

Gln Glu Leu Val Thr Ala Leu Met Cys Asp Leu Arg Arg Pro Ala Ala  
35 40 45

Gly Gly Met Met Asp Leu Ala Tyr Val Cys Glu Trp Glu Lys Trp Ser

50	55	60
Lys Ser Thr His Cys Pro Ser Val Pro Leu Ala Cys Ala Trp Ser Cys		
65	70	75 80
Arg Asn Leu Ile Ala Phe Thr Met Asp Leu Arg Thr Xaa Asp Gln Asp		
	85	90 95
Leu Thr Arg Met Ile His Ile Leu Asp Thr Glu His Pro Trp Asp Leu		
	100	105 110
His Ser Ile Pro Ser Glu His His Glu Ala Ile Thr Cys Leu Glu Trp		
	115	120 125
Asp Gln Ser Gly Ser Arg Leu Leu Ser Ala Asp Ala Asp Gly Gln Ile		
	130	135 140
Lys Cys Trp Ser Met Ala Asp His Leu Ala Asn Ser Trp Glu Ser Ser		
145	150	155 160
Val Gly Ser Leu Val Glu Gly Asp Pro Ile Val Ala Leu Ser Trp Leu		
	165	170 175
His Asn Gly Val Lys Leu Ala Leu His Val Glu Lys Ser Gly Ala Ser		
	180	185 190
Ser Phe Gly Glu Lys Phe Ser Arg Val Lys Phe Ser Pro Val Leu Thr		
	195	200 205
Leu Phe Gly Gly Lys Pro Trp Arg Ala Gly Ser Arg		
210	215	220

&lt;210&gt; 628

&lt;211&gt; 119

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (115)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (117)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 628

Pro Ala Ser Val Glu Val Tyr His Asp Ser Leu Cys Arg Lys Ile Trp



587

1                      5                      10                      15  
 Arg Glu Asp Asp Lys Trp His Val Ile Phe Arg Ala Asp Gly Trp Glu  
                     20                      25                      30  
 Gln His Ile Thr Ala Arg Tyr Leu Val Gly Ala Asp Gly Ala Asn Ser  
                     35                      40                      45  
 Met Val Arg Arg His Leu Tyr Pro Asp His Gln Ile Arg Lys Tyr Val  
                     50                      55                      60  
 Ala Ile Gln Gln Trp Phe Ala Glu Lys His Pro Val Pro Phe Tyr Ser  
                     65                      70                      75                      80  
 Cys Ile Phe Asp Asn Ser Ile Thr Asn Cys Tyr Ser Trp Ser Ile Ser  
                     85                      90                      95  
 Lys Asp Gly Tyr Phe Ile Phe Gly Gly Ala Tyr Pro Met Glu Arg Arg  
                     100                      105                      110  
 Ser Asp Xaa Phe Xaa Asp Ala  
                     115

<210> 629  
 <211> 39  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (30)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (31)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 629  
 Phe Gly Glu Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg Tyr  
                     1                      5                      10                      15  
 Ser Ile Val Ser Met Leu Thr Thr Cys Arg Tyr Ser Leu Xaa Xaa His  
                     20                      25                      30  
 Met Lys Lys Val Ser Ser Cys  
                     35

&lt;210&gt; 630

&lt;211&gt; 267

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 630

Ser Ala Ala Leu Pro Gln Pro Thr Pro Pro Leu Thr Leu Pro Gln Ser  
1 5 10 15

Met Val Asn Thr Lys Pro Glu Lys Thr Glu Glu Asp Ser Glu Glu Val  
20 25 30

Arg Glu Gln Lys His Lys Thr Phe Val Glu Lys Tyr Glu Lys Gln Ile  
35 40 45

Lys His Phe Gly Met Leu Arg Arg Trp Asp Asp Ser Gln Lys Tyr Leu  
50 55 60

Ser Asp Asn Val His Leu Val Cys Glu Glu Thr Ala Asn Tyr Leu Val  
65 70 75 80

Ile Trp Cys Ile Asp Leu Glu Val Glu Glu Lys Cys Ala Leu Met Glu  
85 90 95

Gln Val Ala His Gln Thr Ile Val Met Gln Phe Ile Leu Glu Leu Ala  
100 105 110

Lys Ser Leu Lys Val Asp Pro Arg Ala Cys Phe Arg Gln Phe Phe Thr  
115 120 125

Lys Ile Lys Thr Ala Asp Arg Gln Tyr Met Glu Gly Phe Asn Asp Glu  
130 135 140

Leu Glu Ala Phe Lys Glu Arg Val Arg Gly Arg Ala Lys Leu Arg Ile  
145 150 155 160

Glu Lys Ala Met Lys Glu Tyr Glu Glu Glu Glu Arg Lys Lys Arg Leu  
165 170 175

Gly Pro Gly Gly Leu Asp Pro Val Glu Val Tyr Glu Ser Leu Pro Glu  
180 185 190

Glu Leu Gln Lys Cys Phe Asp Val Lys Asp Val Gln Met Leu Gln Asp  
195 200 205

Ala Ile Ser Lys Met Asp Pro Thr Asp Ala Lys Tyr His Met Gln Arg  
210 215 220

Cys Ile Asp Ser Gly Leu Trp Val Pro Asn Ser Lys Ala Ser Glu Ala  
225 230 235 240

Pro Lys Thr Gly Asp Glu Lys Asp Val Ser Val  
260 265

```
<210> 631
<211> 207
<212> PRT
<213> Homo sapiens
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<220>  
<221> SITE  
<222> (164)  
<223> Xaa equals any of the naturally occurring L-amino acids
```

<400> 631  
Pro Thr Gly Thr Gly Ser Gly Val Pro Gly Leu Gly Arg Asn Gly Gly  
1 5 10 15

Arg Glu Gly Ala Pro Gly Thr Met Gly Leu Leu Thr Ile Leu Lys Lys  
20 25 30

Met Lys Gln Lys Glu Arg Glu Leu Arg Leu Leu Met Leu Gly Leu Asp  
35 40 45

Asn Ala Gly Lys Thr Thr Ile Leu Lys Lys Phe Asn Gly Glu Asp Ile  
50 55 60

Asp Thr Ile Ser Pro Thr Leu Gly Phe Asn Ile Lys Thr Leu Glu His  
65                      70                      75                      80

Arg Gly Phe Lys Leu Asn Ile Trp Asp Val Gly Gly Gln Lys Ser Leu  
85 90 95

Arg Ser Tyr Trp Arg Asn Tyr Phe Glu Ser Thr Asp Gly Leu Ile Trp  
100 105 110

Val Val Asp Ser Ala Asp Arg Gln Arg Met Gln Asp Cys Gln Arg Glu  
115 120 125

Leu Gln Ser Leu Leu Val Glu Glu Arg Leu Ala Gly Ala Thr Leu Leu  
130 135 140

Ile Phe Ala Asn Lys Gln Asp Leu Pro Gly Ala Leu Ser Ser Asn Ala  
145 150 155 160

Ile Arg Glu Xaa Leu Glu Leu Asp Ser Ile Arg Ser His His Trp Cys

590

165 170 175  
 Ile Gln Gly Cys Ser Ala Val Thr Gly Glu Asn Leu Leu Pro Gly Ile  
 180 185 190

Asp Trp Leu Leu Asp Asp Ile Ser Ser Arg Ile Phe Thr Ala Asp  
 195 200 205

&lt;210&gt; 632

&lt;211&gt; 79

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (54)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (60)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (61)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (73)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 632

Lys Asn Asn Lys Lys Asp Gln Gln Asn Gly Ile Cys Ser His Thr Met  
 1 5 10 15

Ile Lys Thr Tyr Leu Arg Thr Ala Leu Phe Met Gly Lys Arg Ser Leu  
 20 25 30

Ile Asp Ser Gln Phe His Arg Leu Tyr Arg Arg His Gly Leu Gly Arg  
 35 40 45

Pro Gln Gly Asn Leu Xaa Ser Met Val Glu Gly Xaa Xaa Gly Ser Met  
 50 55 60

His His Leu His Trp Pro Glu Gln Xaa Glu Arg Glu Gln Ile Trp  
 65 70 75

<210> 633  
 <211> 293  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (249)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (282)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 633  
 Trp Ser Pro Ser Pro Pro Ala Thr Pro Glu Gln Gly Leu Ser Ala Phe  
     1                    5                    10                    15  
 Tyr Leu Ser Tyr Phe Asp Met Leu Tyr Pro Glu Asp Ser Ser Trp Ala  
           20                    25                    30  
 Ala Lys Ala Pro Gly Ala Ser Ser Arg Glu Glu Pro Pro Glu Glu Pro  
       35                    40                    45  
 Glu Gln Cys Pro Val Ile Asp Ser Gln Ala Pro Ala Gly Ser Leu Asp  
     50                    55                    60  
 Leu Val Pro Gly Gly Leu Thr Leu Glu Glu His Ser Leu Glu Gln Val  
     65                    70                    75                    80  
 Gln Ser Met Val Val Gly Glu Val Leu Lys Asp Ile Glu Thr Ala Cys  
           85                    90                    95  
 Lys Leu Leu Asn Ile Thr Ala Asp Pro Met Asp Trp Ser Pro Ser Asn  
       100                    105                    110  
 Val Gln Lys Trp Leu Leu Trp Thr Glu His Gln Tyr Arg Leu Pro Pro  
       115                    120                    125  
 Met Gly Lys Ala Phe Gln Glu Leu Ala Gly Lys Glu Leu Cys Ala Met  
     130                    135                    140  
 Ser Glu Glu Gln Phe Arg Gln Arg Ser Pro Leu Gly Gly Asp Val Leu  
     145                    150                    155                    160  
 His Ala His Leu Asp Ile Trp Lys Ser Ala Ala Trp Met Lys Glu Arg  
       165                    170                    175

Thr Ser Pro Gly Ala Ile His Tyr Cys Ala Ser Thr Ser Glu Glu Ser  
180 185 190

Trp Thr Asp Ser Glu Val Asp Ser Ser Cys Ser Gly Gln Pro Ile His  
195 200 205

Leu Trp Gln Phe Leu Lys Glu Leu Leu Leu Lys Pro His Ser Tyr Gly  
210 215 220

Arg Phe Ile Arg Trp Leu Asn Lys Glu Lys Gly Ile Phe Lys Ile Glu  
225 230 235 240

Asp Ser Ala Gln Val Ala Arg Leu Xaa Gly Ile Arg Lys Asn Arg Pro  
245 250 255

Ala Met Asn Tyr Asp Lys Leu Ser Arg Ser Ile Arg Gln Tyr Tyr Lys  
260 265 270

Lys Gly Ile Ile Arg Lys Pro Asp Ile Xaa Gln Arg Leu Val Tyr Gln  
275 280 285

Phe Val His Pro Ile  
290

<210> 634  
<211> 227  
<212> PRT  
<213> Homo sapiens

<400> 634

Pro Ala Gly Thr Gly Pro Glu Phe Pro Gly Arg Pro Thr Arg Pro Ala  
1 5 10 15

Glu Glu Glu Glu Glu Glu Asp Glu Glu Glu Glu Glu Glu Glu  
20 25 30

Glu Glu Glu Glu Glu Pro Gln Gln Arg Gly Gln Gly Glu Lys Ser Ala  
35 40 45

Thr Pro Ser Arg Lys Ile Leu Asp Pro Asn Thr Gly Glu Pro Ala Pro  
50 55 60

Val Leu Ser Ser Pro Pro Pro Ala Asp Val Ser Thr Phe Leu Ala Phe  
65 70 75 80

Pro Ser Pro Glu Lys Leu Leu Arg Leu Gly Pro Lys Ser Ser Val Leu  
85 90 95

Ile Ala Gln Gln Thr Asp Thr Ser Asp Pro Glu Lys Val Val Ser Ala

593

100	105	110
Phe Leu Lys Val Ser Ser Val	Phe Lys Asp Glu Ala Thr Val Arg Met	
115	120	125
Ala Val Gln Asp Ala Val Asp Ala Leu Met Gln Lys Ala Phe Asn Ser		
130	135	140
Ser Ser Phe Asn Ser Asn Thr Phe Leu Thr Arg Leu Leu Val His Met		
145	150	155
Gly Leu Leu Lys Ser Glu Asp Lys Val Lys Ala Ile Ala Asn Leu Tyr		
165	170	175
Gly Pro Leu Met Ala Leu Asn His Met Val Gln Gln Asp Tyr Phe Pro		
180	185	190
Lys Ala Leu Ala Pro Leu Leu Leu Ala Phe Val Thr Lys Pro Asn Ser		
195	200	205
Ala Leu Glu Ser Cys Ser Phe Ala Arg His Ser Leu Leu Gln Thr Leu		
210	215	220
Tyr Lys Val		
225		

<210> 635  
 <211> 126  
 <212> PRT  
 <213> Homo sapiens

<400> 635
Thr Ser Gly Cys Ile Ser Asn Gly Lys Met Ser Ser Asn Val Pro Ala
1 5 10 15
Asp Met Ile Asn Leu Arg Leu Ile Leu Val Ser Gly Lys Thr Lys Glu
20 25 30
Phe Leu Phe Ser Pro Asn Asp Ser Ala Ser Asp Ile Ala Lys His Val
35 40 45
Tyr Asp Asn Trp Pro Met Asp Trp Glu Glu Glu Gln Val Ser Ser Pro
50 55 60
Asn Ile Leu Arg Leu Ile Tyr Gln Gly Arg Phe Leu His Gly Asn Val
65 70 75 80
Thr Leu Gly Ala Leu Lys Leu Pro Phe Gly Lys Thr Thr Val Met His
85 90 95

594

Leu Val Ala Arg Glu Thr Leu Pro Glu Pro Asn Ser Gln Gly Gln Arg  
 100 105 110

Asn Arg Glu Lys Thr Gly Glu Ser Asn Cys Cys Val Ile Leu  
 115 120 125

&lt;210&gt; 636

&lt;211&gt; 195

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (96)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 636

Val Ser Gly Phe Ala Gly Pro Ala Ser Leu Ile Ser Met Lys Leu Leu  
 1 5 10 15

Ser Leu Val Ala Val Val Gly Cys Leu Val Pro Pro Ala Glu Ala  
 20 25 30

Asn Lys Ser Ser Glu Asp Ile Arg Cys Lys Cys Ile Cys Pro Pro Tyr  
 35 40 45

Arg Asn Ile Ser Gly His Ile Tyr Asn Gln Asn Val Ser Gln Lys Asp  
 50 55 60

Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val Pro Gly His Asp  
 65 70 75 80

Val Glu Ala Tyr Cys Leu Leu Cys Glu Cys Arg Tyr Glu Glu Arg Xaa  
 85 90 95

Thr Thr Thr Ile Lys Val Ile Ile Val Ile Tyr Leu Ser Val Val Gly  
 100 105 110

Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val Asp Pro Leu Ile  
 115 120 125

Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn Glu Glu Glu Asn  
 130 135 140

Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ser Leu Gly Gly Pro  
 145 150 155 160

Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala Gln Gln Arg Trp



595

165 170 175  
Lys Leu Gln Val Gln Glu Gln Arg Lys Thr Val Phe Asp Arg His Lys  
180 185 190

Met Leu Ser  
195

<210> 637  
<211> 159  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (92)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (115)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (138)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (151)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (156)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 637  
Arg Pro Thr Arg Pro Gly Asn Ser Arg Arg Arg Gly Arg Arg Gly Cys  
1 5 10 15

Trp Arg Leu Leu Gly Phe Gly Ala Ala Ala Ile Met Pro Gly Ile Val  
20 25 30

Glu Leu Pro Thr Leu Glu Asp Leu Lys Val Gln Glu Val Lys Val Ser  
35 40 45

Ser Ser Val Leu Lys Ala Ala Ala His His Tyr Gly Val Gln Cys Asp

596

50                      55                      60  
 Lys Pro Asn Lys Glu Phe Met Leu Cys Arg Trp Glu Glu Lys Asp Pro  
 65                      70                      75                      80  
 Arg Arg Cys Leu Glu Glu Gly Lys Leu Val Asn Xaa Cys Ala Leu Asp  
 85                      90                      95  
 Phe Phe Arg Gln Ile Lys Leu Ser Leu Cys Arg Ala Phe Tyr Arg Leu  
 100                      105                      110  
 Leu Asp Xaa His Arg Leu Leu Arg Pro Ala Val Phe Ser Ser Leu Pro  
 115                      120                      125  
 Gln Thr Ala Gly Gln Phe Asp Asp Val Xaa Gly Ala Thr Gly Met Val  
 130                      135                      140  
 Arg Leu Asn Trp Gly Lys Xaa Ser Ser His Gln Xaa Glu Asn Ser  
 145                      150                      155

&lt;210&gt; 638

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 638

Phe Ser Arg Asp Lys Val Ser Pro Cys Trp Pro Gly Trp Ser Arg Thr  
 1                      5                      10                      15

Pro Gly Leu Arg  
 20

&lt;210&gt; 639

&lt;211&gt; 408

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 639

Thr Trp Gly Gln Thr Pro Cys Ser Pro Gly His Gly Gln Arg Pro Ser  
 1                      5                      10                      15

Ser Thr Cys Leu Thr Val Gly Pro Gly Gly Gly Pro Ser Leu Gly Arg  
 20                      25                      30

Pro Cys Pro Gln Leu Leu Leu Gln Phe Gly Val Leu Phe Cys Thr Ile  
 35                      40                      45

Leu Leu Leu Leu Trp Val Ser Val Phe Leu Tyr Gly Ser Phe Tyr Tyr  
 50 55 60  
 Ser Tyr Met Pro Thr Val Ser His Leu Ser Pro Val His Phe Tyr Tyr  
 65 70 75 80  
 Arg Thr Asp Cys Asp Ser Ser Thr Thr Ser Leu Cys Ser Phe Pro Val  
 85 90 95  
 Ala Asn Val Ser Leu Thr Lys Gly Gly Arg Asp Arg Val Leu Met Tyr  
 100 105 110  
 Gly Gln Pro Tyr Arg Val Thr Leu Glu Leu Glu Leu Pro Glu Ser Pro  
 115 120 125  
 Val Asn Gln Asp Leu Gly Met Phe Leu Val Thr Ile Ser Cys Tyr Thr  
 130 135 140  
 Arg Gly Gly Arg Ile Ile Ser Thr Ser Ser Arg Ser Val Met Leu His  
 145 150 155 160  
 Tyr Arg Ser Asp Leu Leu Gln Met Leu Asp Thr Leu Val Phe Ser Ser  
 165 170 175  
 Leu Leu Leu Phe Gly Phe Ala Glu Gln Lys Gln Leu Leu Glu Val Glu  
 180 185 190  
 Leu Tyr Ala Asp Tyr Arg Glu Asn Ser Tyr Val Pro Thr Thr Gly Ala  
 195 200 205  
 Ile Ile Glu Ile His Ser Lys Arg Ile Gln Leu Tyr Gly Ala Tyr Leu  
 210 215 220  
 Arg Ile His Ala His Phe Thr Gly Leu Arg Tyr Leu Leu Tyr Asn Phe  
 225 230 235 240  
 Pro Met Thr Cys Ala Phe Ile Gly Val Ala Ser Asn Phe Thr Phe Leu  
 245 250 255  
 Ser Val Ile Val Leu Phe Ser Tyr Met Gln Trp Val Trp Gly Gly Ile  
 260 265 270  
 Trp Pro Arg His Arg Phe Ser Leu Gln Val Asn Ile Arg Lys Arg Asp  
 275 280 285  
 Asn Ser Arg Lys Glu Val Gln Arg Arg Ile Ser Ala His Gln Pro Gly  
 290 295 300  
 Pro Glu Gly Gln Glu Glu Ser Thr Pro Gln Ser Asp Val Thr Glu Asp  
 305 310 315 320

598

Gly Glu Ser Pro Glu Asp Pro Ser Gly Thr Glu Gly Gln Leu Ser Glu  
325 330 335

Glu Glu Lys Pro Asp Gln Gln Pro Leu Ser Gly Glu Glu Glu Leu Glu  
340 345 350

Pro Glu Ala Ser Asp Gly Ser Gly Ser Trp Glu Asp Ala Ala Leu Leu  
355 360 365

Thr Glu Ala Asn Leu Pro Ala Pro Ala Pro Ala Ser Ala Ser Ala Pro  
370 375 380

Val Leu Glu Thr Leu Gly Ser Ser Glu Pro Ala Gly Gly Ala Leu Arg  
385 390 395 400

Gln Arg Pro Thr Cys Ser Ser Ser  
405

&lt;210&gt; 640

&lt;211&gt; 288

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (15)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (268)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (271)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (273)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (274)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (276)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (286)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 640

Phe	Ser	Ser	Ser	Ala	Cys	Pro	Ser	Val	Xaa	Ser	Leu	Phe	Val	Xaa	Leu
1				5					10					15	

Gly	Lys	Asn	Pro	His	Asp	Ala	Gln	Gly	His	Pro	Arg	Ala	Ser	Glu	Asp
			20					25						30	

Gln	Pro	Ser	Ser	Gly	Lys	Pro	Val	Thr	Ser	Tyr	Pro	Gly	Glu	Cys	Gly
		35					40					45			

Phe	Val	Phe	Thr	Lys	Glu	Ala	Ser	Leu	Glu	Ile	Arg	Asp	Met	Leu	Leu
	50					55					60				

Ala	Asn	Lys	Val	Pro	Ala	Ala	Ala	Arg	Ala	Gly	Ala	Ile	Ala	Pro	Cys
65					70					75					80

Glu	Val	Thr	Val	Pro	Ala	Gln	Asn	Thr	Gly	Leu	Gly	Pro	Glu	Lys	Thr
			85						90					95	

Ser	Phe	Phe	Gln	Ala	Leu	Gly	Ile	Thr	Lys	Ile	Ser	Arg	Gly	Thr	
		100					105						110		

Ile	Glu	Ile	Leu	Ser	Asp	Val	Gln	Leu	Ile	Lys	Thr	Gly	Asp	Lys	Val
	115						120					125			

Gly	Ala	Ser	Glu	Ala	Thr	Leu	Leu	Asn	Met	Leu	Asn	Ile	Ser	Pro	Phe
	130					135						140			

Ser	Phe	Gly	Leu	Ile	Ile	Gln	Gln	Val	Phe	Asp	Asn	Gly	Ser	Ile	Tyr
145				150						155				160	

Asn	Pro	Glu	Val	Leu	Asp	Ile	Thr	Glu	Glu	Thr	Leu	His	Ser	Arg	Phe
			165						170					175	

Leu	Glu	Gly	Val	Arg	Asn	Val	Ala	Ser	Val	Cys	Leu	Gln	Ile	Gly	Tyr
		180						185					190		

600

Pro Thr Val Ala Ser Val Pro His Ser Ile Ile Asn Gly Tyr Lys Arg  
 195 200 205

Val Leu Ala Leu Ser Val Glu Thr Asp Tyr Thr Phe Pro Leu Ala Glu  
 210 215 220

Lys Val Lys Ala Phe Leu Ala Asp Pro Ser Ala Phe Val Ala Ala Ala  
 225 230 235 240

Pro Val Ala Ala Ala Thr Thr Ala Ala Pro Ala Ala Ala Ala Pro  
 245 250 255

Ala Lys Val Glu Ala Lys Glu Glu Ser Glu Glu Xaa Asp Glu Xaa Ile  
 260 265 270

Xaa Xaa Ser Xaa Ile Ser Lys Ser Asn Asn Ser Ser Gln Xaa Ile Val  
 275 280 285

&lt;210&gt; 641

&lt;211&gt; 444

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (34)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 641

Asn Glu Gln Asp Asn Cys Val Leu Ile His Asp Val Asp Gln Arg Asn  
 1 5 10 15

Ser Asp Lys Asp Ile Phe Gly Asp Ala Cys Asp Asn Cys Leu Ser Val  
 20 25 30

Leu Xaa Asn Asp Gln Lys Asp Thr Asp Gly Asp Gly Arg Gly Asp Ala  
 35 40 45

Cys Asp Asp Asp Met Asp Gly Asp Gly Ile Lys Asn Ile Leu Asp Asn  
 50 55 60

Cys Pro Lys Phe Pro Asn Arg Asp Gln Arg Asp Lys Asp Gly Asp Gly  
 65 70 75 80

Val Gly Asp Ala Cys Asp Ser Cys Pro Asp Val Ser Asn Pro Asn Gln  
 85 90 95

601

Ser Asp Val Asp Asn Asp Leu Val Gly Asp Ser Cys Asp Thr Asn Gln  
 100 105 110  
 Asp Ser Asp Gly Asp Gly His Gln Asp Ser Thr Asp Asn Cys Pro Thr  
 115 120 125  
 Val Ile Asn Ser Ala Gln Leu Asp Thr Asp Lys Asp Gly Ile Gly Asp  
 130 135 140  
 Glu Cys Asp Asp Asp Asp Asn Asp Gly Ile Pro Asp Leu Val Pro  
 145 150 155 160  
 Pro Gly Pro Asp Asn Cys Arg Leu Val Pro Asn Pro Ala Gln Glu Asp  
 165 170 175  
 Ser Asn Ser Asp Gly Val Gly Asp Ile Cys Glu Ser Asp Phe Asp Gln  
 180 185 190  
 Asp Gln Val Ile Asp Arg Ile Asp Val Cys Pro Glu Asn Ala Glu Val  
 195 200 205  
 Thr Leu Thr Asp Phe Arg Ala Tyr Gln Thr Val Val Leu Asp Pro Glu  
 210 215 220  
 Gly Asp Ala Gln Ile Asp Pro Asn Trp Val Val Leu Asn Gln Gly Met  
 225 230 235 240  
 Glu Ile Val Gln Thr Met Asn Ser Asp Pro Gly Leu Ala Val Gly Tyr  
 245 250 255  
 Thr Ala Phe Asn Gly Val Asp Phe Glu Gly Thr Phe His Val Asn Thr  
 260 265 270  
 Gln Thr Asp Asp Asp Tyr Ala Gly Phe Ile Phe Gly Tyr Gln Asp Ser  
 275 280 285  
 Ser Ser Phe Tyr Val Val Met Trp Lys Gln Thr Glu Gln Thr Tyr Trp  
 290 295 300  
 Gln Ala Thr Pro Phe Arg Ala Val Ala Glu Pro Gly Ile Gln Leu Lys  
 305 310 315 320  
 Ala Val Lys Ser Lys Thr Gly Pro Gly Glu His Leu Arg Asn Ser Leu  
 325 330 335  
 Trp His Thr Gly Asp Thr Ser Asp Gln Val Arg Leu Leu Trp Lys Asp  
 340 345 350  
 Ser Arg Asn Val Gly Trp Lys Asp Lys Val Ser Tyr Arg Trp Phe Leu  
 355 360 365

602

Gln His Arg Pro Gln Val Gly Tyr Ile Arg Val Arg Phe Tyr Glu Gly  
370 375 380

Ser Glu Leu Val Ala Asp Ser Gly Val Thr Ile Asp Thr Thr Met Arg  
385 390 395 400

Gly Gly Arg Leu Gly Val Phe Cys Phe Ser Gln Glu Asn Ile Ile Trp  
405 410 415

Ser Asn Leu Lys Tyr Arg Cys Asn Asp Thr Ile Pro Glu Asp Phe Gln  
420 425 430

Glu Phe Gln Thr Gln Asn Phe Asp Arg Phe Asp Asn  
435 440

&lt;210&gt; 642

&lt;211&gt; 326

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (296)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 642

Ser Ala Arg Ala Ser Asp Leu Gly Ala Pro Arg Thr Trp Thr Gly Ala  
1 5 10 15

Ala Ala Gly Pro Arg Thr Pro Ser Ala His Ile Pro Val Pro Ala Gln  
20 25 30

Arg Ala Thr Pro Gly Lys Ala Arg Leu Asp Glu Val Met Ala Ala Ala  
35 40 45

Ala Xaa Thr Ser Leu Ser Thr Ser Pro Leu Leu Gly Ala Pro Val  
50 55 60

Ala Ala Phe Ser Pro Glu Pro Gly Leu Glu Pro Trp Lys Glu Ala Leu  
65 70 75 80

Val Arg Pro Pro Gly Ser Tyr Ser Ser Ser Ser Asn Ser Gly Asp Trp  
85 90 95



Gly Trp Asp Leu Ala Ser Asp Gln Ser Ser Pro Ser Thr Pro Ser Pro  
100 105 110

Pro Leu Pro Pro Glu Ala Ala His Phe Leu Phe Gly Glu Pro Thr Leu  
115 120 125

Arg Lys Arg Lys Ser Pro Ala Gln Val Met Phe Gln Cys Leu Trp Lys  
130 135 140

Ser Cys Gly Lys Val Leu Ser Thr Ala Ser Ala Met Gln Arg His Ile  
145 150 155 160

Arg Leu Val His Leu Gly Arg Gln Ala Glu Pro Asp Gln Ser Asp Gly  
165 170 175

Glu Glu Asp Phe Tyr Tyr Thr Glu Leu Asp Val Gly Val Asp Thr Leu  
180 185 190

Thr Asp Gly Leu Ser Ser Leu Thr Pro Val Ser Pro Thr Ala Ser Met  
195 200 205

Pro Pro Ala Phe Pro Arg Leu Glu Leu Pro Glu Leu Leu Glu Pro Pro  
210 215 220

Ala Leu Pro Ser Pro Leu Arg Pro Pro Ala Pro Pro Leu Pro Pro Pro  
225 230 235 240

Pro Val Leu Ser Thr Val Ala Asn Pro Gln Ser Cys His Ser Asp Arg  
245 250 255

Val Tyr Gln Gly Cys Leu Thr Pro Ala Arg Leu Glu Pro Gln Pro Thr  
260 265 270

Glu Val Gly Ala Cys Pro Pro Ala Leu Ser Ser Arg Ile Gly Val Thr  
275 280 285

Leu Arg Lys Pro Arg Gly Asp Xaa Lys Lys Cys Arg Lys Val Tyr Gly  
290 295 300

Met Glu Arg Arg Asp Leu Trp Cys Thr Ala Cys Arg Trp Lys Lys Ala  
305 310 315 320

Cys Gln Arg Phe Leu Asp  
325

&lt;210&gt; 643

&lt;211&gt; 129

&lt;212&gt; PRT

<213> Homo sapiens

<220>  
<221> SITE  
<222> (9)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (10)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (14)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (18)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (19)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (24)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (38)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (94)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (103)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 643  
Asp Val Arg Leu Ser Gly Arg Asn Xaa Xaa Val Asp Val Xaa Asp His  
1 5 10 15

605

Gln Xaa Xaa Leu Leu Glu Gln Xaa Asp Leu Leu Ala Gly Leu Ile Ser  
                   20                  25                  30  
 Asn Ser Ser Asp Ala Xaa Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp  
                   35                  40                  45  
 Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu Ile Pro  
                   50                  55                  60  
 Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Gly Tyr Arg Asp Arg Met  
                   65                  70                  75                  80  
 Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Xaa Ser Gly  
                   85                  90                  95  
 Thr Lys Ala Phe Met Glu Xaa Leu Gln Ala Gly Ala Asp Ile Ser Met  
                   100                  105                  110  
 Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Arg  
                   115                  120                  125  
 Arg

&lt;210&gt; 644

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 644

Ser Thr His Ala Ser Ala Ser Arg Arg Leu Leu Xaa Asp Val Cys Gln  
                   1                  5                  10                  15  
 Asp Cys Ile Gln Met Val Thr Asp Ile Gln Thr Ala Val Arg Thr Asn  
                   20                  25                  30  
 Ser Thr Phe Val Glu Ala Leu Val Asp His Ala Lys Ala Gln Cys Asp  
                   35                  40                  45  
 Leu Leu Gly Pro Gly Met Ala Asp Met Cys Lys Asn Tyr Ile Asn Gln  
                   50                  55                  60  
 Tyr Ser Asp Ile Ala Val Gln Met Met Met His Met Gln Pro Lys Glu  
                   65                  70                  75                  80

606

Ile Cys Gly Leu Val Gly Phe Cys Asp Gln Val Lys Glu Met Pro Met  
                     85                    90                    95

Gln Thr Leu Ile Pro Ala Lys Ala Val Ser Glu Asn Val Ile Pro Ala  
                     100                    105                    110

Leu Glu Leu Val Glu Pro Ile Lys Asp Thr Val Gln Ala Lys Thr  
                     115                    120                    125

Ser Val Ser Cys Gly Asp Met Arg Val Thr Trp Leu Lys Glu Val Ala  
                     130                    135                    140

Lys Leu His Trp Thr Thr Thr Gly Leu Arg Lys Lys  
                     145                    150                    155

<210> 645  
 <211> 115  
 <212> PRT  
 <213> Homo sapiens

<400> 645  
 Ala Asp Pro Gly Val Gly Ala Val Pro Gly Leu Ala Ala Asp Leu Ala  
   1                    5                    10                    15

Thr Ala Ala Arg Ser Leu Gly Pro Ala Leu Val Leu Asp Leu Gly Arg  
                     20                    25                    30

Pro Pro Ser Pro Asp Pro His Glu Gly Pro Ser Pro Ser Pro Arg Arg  
                     35                    40                    45

Ser Pro Asp Leu Val Arg Gly Pro Gly Pro Gly Leu Gly Pro Gly Val  
                     50                    55                    60

Leu Pro Gln Cys Pro Arg Gly Asn Pro Asn Pro Gly Arg Asp Arg Arg  
   65                    70                    75                    80

Val Pro Pro Ser Leu Leu Lys Arg Lys Glu Arg Cys Pro Leu Lys Lys  
                     85                    90                    95

Met Val Met Ser Gly Asn Pro Arg His Ile Thr Leu Ile His Lys Trp  
                     100                    105                    110

Asp Leu Gly  
                     115

<210> 646

607

&lt;211&gt; 153

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (127)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 646

Tyr Met Pro Asn Gly Ser Leu Asn Glu Leu Leu His Arg Lys Thr Glu  
 1 5 10 15

Tyr Pro Asp Val Ala Trp Pro Leu Arg Phe Arg Ile Leu His Glu Ile  
 20 25 30

Ala Leu Gly Val Asn Tyr Leu His Asn Met Thr Pro Pro Leu Leu His  
 35 40 45

His Asp Leu Lys Thr Gln Asn Ile Leu Leu Asp Asn Glu Phe His Val  
 50 55 60

Lys Ile Ala Asp Phe Gly Leu Ser Lys Trp Arg Met Met Ser Leu Ser  
 65 70 75 80

Gln Ser Arg Ser Ser Lys Ser Ala Pro Glu Gly Gly Thr Ile Ile Tyr  
 85 90 95

Met Pro Pro Glu Asn Tyr Glu Pro Gly Gln Lys Ser Arg Ala Ser Ile  
 100 105 110

Lys His Asp Ile Tyr Ser Tyr Ala Val Ile Thr Trp Glu Val Xaa Ser  
 115 120 125

Arg Lys Gln Pro Phe Glu Asp Val Thr Asn Pro Leu Gln Ile Met Tyr  
 130 135 140

Ser Val Ser Gln Gly His Trp Thr Gly  
 145 150

&lt;210&gt; 647

&lt;211&gt; 220

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 647

Ala Ser Glu Gln Gly Ala Val Gly Gln Gly Gly Leu Ala Gly Val Pro  
 1 5 10 15

608

Thr Leu Thr Ser Leu Pro Ser Ser Cys Pro Glu Pro Arg Pro Ser Met  
 20 25 30  
 Asp Ala Val Asp Ala Thr Met Glu Lys Leu Arg Ala Gln Cys Leu Ser  
 35 40 45  
 Arg Gly Ala Ser Gly Ile Gln Gly Leu Ala Arg Phe Phe Arg Gln Leu  
 50 55 60  
 Asp Arg Asp Gly Ser Arg Ser Leu Asp Ala Asp Glu Phe Arg Gln Gly  
 65 70 75 80  
 Leu Ala Lys Leu Gly Leu Val Leu Asp Gln Ala Glu Ala Glu Gly Val  
 85 90 95  
 Cys Arg Lys Trp Asp Arg Asn Gly Ser Gly Thr Leu Asp Leu Glu Glu  
 100 105 110  
 Phe Leu Arg Ala Leu Arg Pro Pro Met Ser Gln Ala Arg Glu Ala Val  
 115 120 125  
 Ile Ala Ala Ala Phe Ala Lys Leu Asp Arg Ser Gly Asp Gly Val Val  
 130 135 140  
 Thr Val Asp Asp Leu Arg Gly Val Tyr Ser Gly Arg Ala His Pro Lys  
 145 150 155 160  
 Val Arg Ser Gly Glu Trp Thr Glu Asp Glu Val Leu Arg Arg Phe Leu  
 165 170 175  
 Asp Asn Phe Asp Ser Ser Glu Lys Asp Gly Gln Val Thr Leu Ala Glu  
 180 185 190  
 Phe Gln Asp Tyr Tyr Ser Gly Val Ser Ala Ser Met Asn Thr Asp Glu  
 195 200 205  
 Glu Phe Val Ala Met Met Thr Ser Ala Trp Gln Leu  
 210 215 220

&lt;210&gt; 648

&lt;211&gt; 118

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 648

Asp Asn Arg Thr Leu Thr Lys Gly Pro Asp Thr Val Gly Thr Met Gly  
 1 5 10 15

Gln Cys Arg Ser Ala Asn Ala Glu Asp Ala Gln Glu Phe Ser Asp Val

609

20 25 30  
 Glu Arg Ala Ile Glu Thr Leu Ile Lys Asn Phe His Gln Tyr Ser Val  
 35 40 45  
 Glu Gly Gly Lys Glu Thr Leu Thr Pro Ser Glu Leu Arg Asp Leu Val  
 50 55 60  
 Thr Gln Gln Leu Pro His Leu Met Pro Ser Asn Cys Gly Leu Glu Glu  
 65 70 75 80  
 Lys Ile Ala Asn Leu Gly Ser Cys Asn Asp Ser Lys Leu Glu Phe Arg  
 85 90 95  
 Ser Phe Trp Glu Leu Ile Gly Glu Ala Ala Lys Ser Val Lys Leu Glu  
 100 105 110  
 Arg Pro Val Arg Gly His  
 115

<210> 649  
 <211> 309  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (77)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (160)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 649  
 Asp His His Gln Gly Ala Glu Ser Val Pro Gly Ile Gly Val Ser Pro  
 1 5 10 15  
 Thr Ser Ser Ser Ser Cys Pro Pro Thr Ser Cys Thr Gln Pro Val Thr  
 20 25 30  
 Thr Trp Ser Pro Gly Leu Arg Val Glu Ser Leu Asp Gly Ala Lys Thr  
 35 40 45  
 Gly Lys Gly Ala Leu Thr Gly Ala Pro Gly Ser Phe Gly Ser Ser Glu  
 50 55 60  
 Phe Leu Thr Gly Leu Arg Asn Thr Ser Glu Ala Arg Xaa Thr Arg Gly

610

65                      70                      75                      80  
 Pro Ile Met Gln Glu Pro Arg Arg Val Thr Pro Cys Leu Gly Lys Arg  
                                  85                      90                      95  
 Gly Val Lys Thr Pro Gln Leu Gln Pro Gly Ser Ala Phe Leu Pro Arg  
                                  100                      105                      110  
 Val Arg Arg Gln Ser Phe Pro Ala Arg Ser Asp Ser Tyr Thr Thr Val  
                                  115                      120                      125  
 Arg Asp Phe Leu Ala Val Pro Arg Thr Ile Ser Ser Ala Ser Ala Thr  
                                  130                      135                      140  
 Leu Ile Met Ala Val Ala Val Ser His Phe Arg Pro Gly Pro Glu Xaa  
 145                                   150                      155                      160  
 Trp Asp Thr Ala Ser Met Ala Ala Ser Lys Val Lys Gln Asp Met Pro  
                                  165                      170                      175  
 Pro Pro Gly Gly Tyr Gly Pro Ile Asp Tyr Lys Arg Asn Leu Pro Arg  
                                  180                      185                      190  
 Arg Gly Leu Ser Gly Tyr Ser Met Leu Ala Ile Gly Ile Gly Thr Leu  
                                  195                      200                      205  
 Ile Tyr Gly His Trp Ser Ile Met Lys Trp Asn Arg Glu Arg Arg Arg  
                                  210                      215                      220  
 Leu Gln Ile Glu Asp Phe Glu Ala Arg Ile Ala Leu Leu Pro Leu Leu  
 225                                   230                      235                      240  
 Gln Ala Glu Thr Asp Arg Arg Thr Leu Gln Met Leu Arg Glu Asn Leu  
                                  245                      250                      255  
 Glu Glu Glu Ala Ile Ile Met Lys Asp Val Pro Asp Trp Lys Val Gly  
                                  260                      265                      270  
 Glu Ser Val Phe His Thr Thr Arg Trp Val Pro Pro Leu Ile Gly Glu  
                                  275                      280                      285  
 Leu Tyr Gly Leu Arg Thr Thr Glu Glu Ala Leu His Ala Ser His Gly  
                                  290                      295                      300  
 Phe Met Trp Tyr Thr  
 305

&lt;210&gt; 650

&lt;211&gt; 286



611

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 650

Ile Pro Thr Leu Ile Thr Ala Phe Val Leu Ala Thr Ser Gln Ala Gln  
1 5 10 15

Ala Gly Trp Leu Gln His Asp Tyr Gly His Leu Ser Val Tyr Arg Lys  
20 25 30

Pro Lys Trp Asn His Leu Val His Lys Phe Val Ile Gly His Leu Lys  
35 40 45

Gly Ala Ser Ala Asn Trp Trp Asn His Arg His Phe Gln His His Ala  
50 55 60

Lys Pro Asn Ile Phe His Lys Asp Pro Asp Val Asn Met Leu His Val  
65 70 75 80

Phe Val Leu Gly Glu Trp Gln Pro Ile Glu Tyr Gly Lys Lys Lys Leu  
85 90 95

Lys Tyr Leu Pro Tyr Asn His Gln His Glu Tyr Phe Phe Leu Ile Gly  
100 105 110

Pro Pro Leu Leu Ile Pro Met Tyr Phe Gln Tyr Gln Ile Ile Met Thr  
115 120 125

Met Ile Val His Lys Asn Trp Val Asp Leu Ala Trp Ala Val Ser Tyr  
130 135 140

Tyr Ile Arg Phe Phe Ile Thr Tyr Ile Pro Phe Tyr Gly Ile Leu Gly  
145 150 155 160

Ala Leu Leu Phe Leu Asn Phe Ile Arg Phe Leu Glu Ser His Trp Phe  
165 170 175

Val Trp Val Thr Gln Met Asn His Ile Val Met Glu Ile Asp Gln Glu  
180 185 190

Ala Tyr Arg Asp Trp Phe Ser Ser Gln Leu Thr Ala Thr Cys Asn Val  
195 200 205

Glu Gln Ser Phe Phe Asn Asp Trp Phe Ser Gly His Leu Asn Phe Gln  
210 215 220

Ile Glu His His Leu Phe Pro Thr Met Pro Arg His Asn Leu His Lys  
225 230 235 240

Ile Ala Pro Leu Val Lys Ser Leu Cys Ala Lys His Gly Ile Glu Tyr  
245 250 255

612

Gln Glu Lys Pro Leu Leu Arg Ala Leu Leu Asp Ile Ile Arg Ser Leu  
                   260                                  265                                  270

Lys Lys Ser Gly Lys Leu Trp Leu Asp Ala Tyr Leu His Lys  
                   275                                  280                                  285

&lt;210&gt; 651

&lt;211&gt; 184

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (35)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (106)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 651

Glu Arg Gly Pro Ile Pro Val Cys Pro His Lys Ala Ala Ser Ser Val  
   1                                  5                                  10                                  15

Ile Ser Leu Leu Arg Ala Glu Leu Arg Leu Tyr Thr Asp Pro His Lys  
                   20                                  25                                  30

Tyr His Xaa Phe Cys Leu Arg Lys Asp Lys Ala His Val Cys Phe Cys  
           35                                  40                                  45

Phe Arg Phe Leu Phe Ser Phe Phe Xaa Glu Ala Leu Trp Arg Ser Met  
   50                                  55                                  60

Phe Leu Leu Ser Phe Leu Xaa Lys Pro Ser Phe Trp Ala Thr Gly Leu  
   65                                  70                                  75                                  80

Ile Leu Ser Thr Ser Ser Phe Pro Pro Phe Ser Ile Val Ser Leu Pro

613

85                      90                      95  
 Pro Ser His Pro Thr Arg Ala Pro Leu Xaa Leu Ser Phe Pro Ser Ser  
                     100                      105                      110  
 Pro Ala Val Ser Phe Leu Arg Ser Gly Thr Lys Leu Ile Phe Arg Arg  
                     115                      120                      125  
 Arg Pro Arg Gln Lys Glu Ala Gly Leu Ser Gln Ser His Asp Asp Leu  
                     130                      135                      140  
 Ser Asn Ala Thr Ala Thr Pro Ser Val Arg Lys Lys Ala Gly Ser Phe  
                     145                      150                      155                      160  
 Ser Arg Arg Leu Ile Lys Arg Phe Ser Phe Lys Ser Lys Pro Lys Ala  
                     165                      170                      175  
 Asn Gly Asn Pro Ser Pro Gln Leu  
                     180

&lt;210&gt; 652

&lt;211&gt; 641

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (438)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 652

Gln Gly Ser Glu Pro Ser Ser Glu Asn Ala Asn Asp Thr Ile Ile Leu  
                     1                      5                      10                      15  
 Arg Asn Leu Asn Pro His Ser Thr Met Asp Ser Ile Leu Gly Ala Leu  
                     20                      25                      30  
 Ala Pro Tyr Ala Val Leu Ser Ser Ser Asn Val Arg Val Ile Lys Asp  
                     35                      40                      45  
 Lys Gln Thr Gln Leu Asn Arg Gly Phe Ala Phe Ile Gln Leu Ser Thr  
                     50                      55                      60  
 Ile Glu Ala Ala Gln Leu Leu Gln Ile Leu Gln Ala Leu His Pro Pro  
                     65                      70                      75                      80  
 Leu Thr Ile Asp Gly Lys Thr Ile Asn Val Glu Phe Ala Lys Gly Ser  
                     85                      90                      95

Lys Arg Asp Met Ala Ser Asn Glu Gly Ser Arg Ile Ser Ala Ala Ser  
100 105 110

Val Ala Ser Thr Ala Ile Ala Ala Ala Gln Trp Ala Ile Ser Gln Ala  
115 120 125

Ser Gln Gly Gly Glu Gly Thr Trp Ala Thr Ser Glu Glu Pro Pro Val  
130 135 140

Asp Tyr Ser Tyr Tyr Gln Gln Asp Glu Gly Tyr Gly Asn Ser Gln Gly  
145 150 155 160

Thr Glu Ser Ser Leu Tyr Ala His Gly Tyr Leu Lys Gly Thr Lys Gly  
165 170 175

Pro Gly Ile Thr Gly Thr Lys Gly Asp Pro Thr Gly Ala Gly Pro Glu  
180 185 190

Ala Ser Leu Glu Pro Gly Ala Asp Ser Val Ser Met Gln Ala Phe Ser  
195 200 205

Arg Ala Gln Pro Gly Ala Ala Pro Gly Ile Tyr Gln Gln Ser Ala Glu  
210 215 220

Ala Ser Ser Ser Gln Gly Thr Ala Ala Asn Ser Gln Ser Tyr Thr Ile  
225 230 235 240

Met Ser Pro Ala Val Leu Lys Ser Glu Leu Gln Ser Pro Thr His Pro  
245 250 255

Ser Ser Ala Leu Pro Pro Ala Thr Ser Pro Thr Ala Gln Glu Ser Tyr  
260 265 270

Ser Gln Tyr Pro Val Pro Asp Val Ser Thr Tyr Gln Tyr Asp Glu Thr  
275 280 285

Ser Gly Tyr Tyr Tyr Asp Pro Gln Thr Gly Leu Tyr Tyr Asp Pro Asn  
290 295 300

Ser Gln Tyr Tyr Tyr Asn Ala Gln Ser Gln Gln Tyr Leu Tyr Trp Asp  
305 310 315 320

Gly Glu Arg Arg Thr Tyr Val Pro Ala Leu Glu Gln Ser Ala Asp Gly  
325 330 335

His Lys Glu Thr Gly Ala Pro Ser Lys Glu Gly Lys Glu Lys Lys Glu  
340 345 350

Lys His Lys Thr Lys Thr Ala Gln Gln Ile Ala Lys Asp Met Glu Arg  
355 360 365

615

Trp Ala Arg Ser Leu Asn Lys Gln Lys Glu Asn Phe Lys Asn Ser Phe  
 370 375 380  
 Gln Pro Ile Ser Ser Leu Arg Asp Asp Glu Arg Arg Glu Ser Ala Thr  
 385 390 395 400  
 Ala Asp Ala Gly Tyr Ala Ile Leu Glu Lys Lys Gly Ala Leu Ala Glu  
 405 410 415  
 Arg Gln His Thr Ser Met Asp Leu Pro Lys Leu Ala Ser Asp Asp Arg  
 420 425 430  
 Pro Ser Pro Pro Arg Xaa Leu Val Ala Ala Tyr Ser Gly Glu Ser Asp  
 435 440 445  
 Ser Glu Glu Glu Gln Glu Arg Gly Gly Pro Glu Arg Glu Glu Lys Leu  
 450 455 460  
 Thr Asp Trp Gln Lys Leu Ala Cys Leu Leu Cys Arg Arg Gln Phe Pro  
 465 470 475 480  
 Ser Lys Glu Ala Leu Ile Arg His Gln Gln Leu Ser Gly Leu His Lys  
 485 490 495  
 Gln Asn Leu Glu Ile His Arg Arg Ala His Leu Ser Glu Asn Glu Leu  
 500 505 510  
 Glu Ala Leu Glu Lys Asn Asp Met Glu Gln Met Lys Tyr Arg Asp Arg  
 515 520 525  
 Ala Ala Glu Arg Arg Glu Lys Tyr Gly Ile Pro Glu Pro Pro Glu Pro  
 530 535 540  
 Lys Arg Arg Lys Tyr Gly Gly Ile Ser Thr Ala Ser Val Asp Phe Glu  
 545 550 555 560  
 Gln Pro Thr Arg Asp Gly Leu Gly Ser Asp Asn Ile Gly Ser Arg Met  
 565 570 575  
 Leu Gln Ala Met Gly Trp Lys Glu Gly Ser Gly Leu Gly Arg Lys Lys  
 580 585 590  
 Gln Gly Ile Val Thr Pro Ile Glu Ala Gln Thr Arg Val Arg Gly Ser  
 595 600 605  
 Gly Leu Gly Ala Arg Gly Ser Ser Tyr Gly Val Thr Ser Thr Glu Ser  
 610 615 620  
 Tyr Lys Glu Thr Leu His Lys Thr Met Val Thr Arg Phe Asn Glu Ala  
 625 630 635 640

616

Gln

&lt;210&gt; 653

&lt;211&gt; 516

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (247)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 653

Xaa	Thr	Arg	Pro	Gly	Arg	Gln	Thr	Arg	Leu	Cys	Arg	Pro	Ala	Ile	Ser
1				5					10					15	

Leu	Leu	Trp	Leu	Val	Thr	Pro	Gly	Val	Pro	Ala	Phe	Ser	Gly	Trp	Gly
			20					25					30		

Arg	Arg	His	Arg	Gly	Arg	Thr	Gly	Arg	Arg	Ala	Met	Ala	Ser	Cys	Val
		35					40					45			

Gly	Ser	Arg	Thr	Leu	Ser	Lys	Asp	Asp	Val	Asn	Tyr	Lys	Met	His	Phe
	50					55					60				

Arg	Met	Ile	Asn	Glu	Gln	Gln	Val	Glu	Asp	Ile	Thr	Ile	Asp	Phe	Phe
65					70					75					80

Tyr	Arg	Pro	His	Thr	Ile	Thr	Leu	Leu	Ser	Phe	Thr	Ile	Val	Ser	Leu
				85					90					95	

Met	Tyr	Phe	Ala	Phe	Thr	Arg	Asp	Asp	Ser	Val	Pro	Glu	Asp	Asn	Ile
		100						105					110		

Trp	Arg	Gly	Ile	Leu	Ser	Val	Ile	Phe	Phe	Phe	Leu	Ile	Ile	Ser	Val
		115					120					125			

Leu	Ala	Phe	Pro	Asn	Gly	Pro	Phe	Thr	Arg	Pro	His	Pro	Ala	Leu	Trp
	130					135					140				

Arg	Met	Val	Phe	Gly	Leu	Ser	Val	Leu	Tyr	Phe	Leu	Phe	Leu	Val	Phe
145					150					155					160

Leu Leu Phe Leu Asn Phe Glu Gln Val Lys Ser Leu Met Tyr Trp Leu  
 165 170 175  
 Asp Pro Asn Leu Arg Tyr Ala Thr Arg Glu Ala Asp Val Met Glu Tyr  
 180 185 190  
 Ala Val Asn Cys His Val Ile Thr Trp Glu Arg Ile Ile Ser His Phe  
 195 200 205  
 Asp Ile Phe Ala Phe Gly His Phe Trp Gly Trp Ala Met Lys Ala Leu  
 210 215 220  
 Leu Ile Arg Ser Tyr Gly Leu Cys Trp Thr Ile Ser Ile Thr Trp Glu  
 225 230 235 240  
 Leu Thr Glu Leu Phe Phe Xaa His Leu Leu Pro Asn Phe Ala Glu Cys  
 245 250 255  
 Trp Trp Asp Gln Val Ile Leu Asp Ile Leu Leu Cys Asn Gly Gly Gly  
 260 265 270  
 Ile Trp Leu Gly Met Val Val Cys Arg Phe Leu Glu Met Arg Thr Tyr  
 275 280 285  
 His Trp Ala Ser Phe Lys Asp Ile His Thr Thr Thr Gly Lys Ile Lys  
 290 295 300  
 Arg Ala Val Leu Gln Phe Thr Pro Ala Ser Trp Thr Tyr Val Arg Trp  
 305 310 315 320  
 Phe Asp Pro Lys Ser Ser Phe Gln Arg Val Ala Gly Val Tyr Leu Phe  
 325 330 335  
 Met Ile Ile Trp Gln Leu Thr Glu Leu Asn Thr Phe Phe Leu Lys His  
 340 345 350  
 Ile Phe Val Phe Gln Ala Ser His Pro Leu Ser Trp Gly Arg Ile Leu  
 355 360 365  
 Phe Ile Gly Gly Ile Thr Ala Pro Thr Val Arg Gln Tyr Tyr Ala Tyr  
 370 375 380  
 Leu Thr Asp Thr Gln Cys Lys Arg Val Gly Thr Gln Cys Trp Val Phe  
 385 390 395 400  
 Gly Val Ile Gly Phe Leu Glu Ala Ile Val Cys Ile Lys Phe Gly Gln  
 405 410 415  
 Asp Leu Phe Ser Lys Thr Gln Ile Leu Tyr Val Val Leu Trp Leu Leu  
 420 425 430

618

Cys Val Ala Phe Thr Thr Phe Leu Cys Leu Tyr Gly Met Ile Trp Tyr  
 435 440 445

Ala Glu His Tyr Gly His Arg Glu Lys Thr Tyr Ser Glu Cys Glu Asp  
 450 455 460

Gly Thr Tyr Ser Pro Glu Ile Ser Trp His His Arg Lys Gly Thr Lys  
 465 470 475 480

Gly Ser Glu Asp Ser Pro Pro Lys His Ala Gly Asn Asn Glu Ser His  
 485 490 495

Ser Ser Arg Arg Arg Asn Arg His Ser Lys Ser Lys Val Thr Asn Gly  
 500 505 510

Val Gly Lys Lys  
 515

<210> 654

<211> 663

<212> PRT

<213> Homo sapiens

<400> 654

Leu Glu Cys Arg Glu Ala His Ile Arg Asp Val Pro Val Val Arg Leu  
 1 5 10 15

Pro Ala Asp Ser Pro Ile Pro Glu Arg Gly Asp Leu Ser Cys Arg Met  
 20 25 30

His Thr Cys Phe Asp Val Tyr Arg Cys Gly Phe Asn Pro Lys Asn Lys  
 35 40 45

Ile Lys Val Tyr Ile Tyr Ala Leu Lys Lys Tyr Val Asp Asp Phe Gly  
 50 55 60

Val Ser Val Ser Asn Thr Ile Ser Arg Glu Tyr Asn Glu Leu Leu Met  
 65 70 75 80

Ala Ile Ser Asp Ser Asp Tyr Tyr Thr Asp Asp Ile Asn Arg Ala Cys  
 85 90 95

Leu Phe Val Pro Ser Ile Asp Val Leu Asn Gln Asn Thr Leu Arg Ile  
 100 105 110

Lys Glu Thr Ala Gln Ala Met Ala Gln Leu Ser Arg Trp Asp Arg Gly  
 115 120 125

Thr Asn His Leu Leu Phe Asn Met Leu Pro Gly Gly Pro Pro Asp Tyr



619

130	135	140
Asn Thr Ala Leu Asp Val Pro Arg Asp Arg Ala Leu Leu Ala Gly Gly		
145	150	155 160
Gly Phe Ser Thr Trp Thr Tyr Arg Gln Gly Tyr Asp Val Ser Ile Pro		
	165	170 175
Val Tyr Ser Pro Leu Ser Ala Glu Val Asp Leu Pro Glu Lys Gly Pro		
	180	185 190
Gly Pro Arg Gln Tyr Phe Leu Leu Ser Ser Gln Val Gly Leu His Pro		
	195	200 205
Glu Tyr Arg Glu Asp Leu Glu Ala Leu Gln Val Lys His Gly Glu Ser		
	210	215 220
Val Leu Val Leu Asp Lys Cys Thr Asn Leu Ser Glu Gly Val Leu Ser		
	225	230 235 240
Val Arg Lys Arg Cys His Lys His Gln Val Phe Asp Tyr Pro Gln Val		
	245	250 255
Leu Gln Glu Ala Thr Phe Cys Val Val Leu Arg Gly Ala Arg Leu Gly		
	260	265 270
Gln Ala Val Leu Ser Asp Val Leu Gln Ala Gly Cys Val Pro Val Val		
	275	280 285
Ile Ala Asp Ser Tyr Ile Leu Pro Phe Ser Glu Val Leu Asp Trp Lys		
	290	295 300
Arg Ala Ser Val Val Val Pro Glu Glu Lys Met Ser Asp Val Tyr Ser		
	305	310 315 320
Ile Leu Gln Ser Ile Pro Gln Arg Gln Ile Glu Glu Met Gln Arg Gln		
	325	330 335
Ala Arg Trp Phe Trp Glu Ala Tyr Phe Gln Ser Ile Lys Ala Ile Ala		
	340	345 350
Leu Ala Thr Leu Gln Ile Ile Asn Asp Arg Ile Tyr Pro Tyr Ala Ala		
	355	360 365
Ile Ser Tyr Glu Glu Trp Asn Asp Pro Pro Ala Val Lys Trp Gly Ser		
	370	375 380
Val Ser Asn Pro Leu Phe Leu Pro Leu Ile Pro Pro Gln Ser Gln Gly		
	385	390 395 400
Phe Thr Ala Ile Val Leu Thr Tyr Asp Arg Val Glu Ser Leu Phe Arg		

620

405	410	415
Val Ile Thr Glu Val Ser Lys Val Pro Ser Leu Ser Lys Leu Leu Val		
420	425	430
Val Trp Asn Asn Gln Asn Lys Asn Pro Pro Glu Asp Ser Leu Trp Pro		
435	440	445
Lys Ile Arg Val Pro Leu Lys Val Val Arg Thr Ala Glu Asn Lys Leu		
450	455	460
Ser Asn Arg Phe Phe Pro Tyr Asp Glu Ile Glu Thr Glu Ala Val Leu		
465	470	475
Ala Ile Asp Asp Asp Ile Ile Met Leu Thr Ser Asp Glu Leu Gln Phe		
485	490	495
Gly Tyr Glu Val Trp Arg Glu Phe Pro Asp Arg Leu Val Gly Tyr Pro		
500	505	510
Gly Arg Leu His Leu Trp Asp His Glu Met Asn Lys Trp Lys Tyr Glu		
515	520	525
Ser Glu Trp Thr Asn Glu Val Ser Met Val Leu Thr Gly Ala Ala Phe		
530	535	540
Tyr His Lys Tyr Phe Asn Tyr Leu Tyr Thr Tyr Lys Met Pro Gly Asp		
545	550	555
Ile Lys Asn Trp Val Asp Ala His Met Asn Cys Glu Asp Ile Ala Met		
565	570	575
Asn Phe Leu Val Ala Asn Val Thr Gly Lys Ala Val Ile Lys Val Thr		
580	585	590
Pro Arg Lys Lys Phe Lys Cys Pro Glu Cys Thr Ala Ile Asp Gly Leu		
595	600	605
Ser Leu Asp Gln Thr His Met Val Glu Arg Ser Glu Cys Ile Asn Lys		
610	615	620
Phe Ala Ser Val Phe Gly Thr Met Pro Leu Lys Val Val Glu His Arg		
625	630	635
Ala Asp Pro Val Leu Tyr Lys Asp Asp Phe Pro Glu Lys Leu Lys Ser		
645	650	655
Phe Pro Asn Ile Gly Ser Leu		
660		

621

<210> 655  
<211> 97  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (38)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (91)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 655  
Ala Thr Gln Leu Leu Ser Ser Phe Ser Val Gly Pro Leu Leu Gln Ile  
1 5 10 15  
Thr Phe Tyr Glu Asp Lys Asn Phe Gln Gly Arg Arg Tyr Asp Cys Asp  
20 25 30  
Cys Asp Cys Ala Asp Xaa His Thr Tyr Leu Ser Arg Cys Asn Ser Ile  
35 40 45  
Lys Val Glu Gly Gly Thr Trp Ala Val Tyr Glu Arg Pro Asn Phe Ala  
50 55 60  
Gly Tyr Met Tyr Ile Leu Pro Gln Gly Glu Tyr Pro Glu Tyr Gln Arg  
65 70 75 80  
Trp Met Gly Leu Asn Asp Arg Leu Ser Ser Xaa Arg Ala Val Ser Ser  
85 90 95

Ala

<210> 656  
<211> 167  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (59)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

622

&lt;221&gt; SITE

&lt;222&gt; (73)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 656

Asp Ala Asp Leu Val Ile Trp Asp Pro Asp Ser Val Lys Thr Ile Ser  
 1 5 10 15

Ala Lys Thr His Asn Ser Ser Leu Glu Tyr Asn Ile Phe Glu Gly Met  
 20 25 30

Glu Cys Arg Gly Ser Pro Leu Val Val Ile Ser Gln Gly Lys Ile Val  
 35 40 45

Leu Glu Asp Gly Thr Leu His Val Thr Glu Xaa Ser Gly Arg Tyr Ile  
 50 55 60

Pro Arg Lys Pro Phe Pro Asp Phe Xaa Tyr Lys Arg Ile Lys Ala Arg  
 65 70 75 80

Ser Arg Leu Ala Glu Leu Arg Gly Val Pro Arg Gly Leu Tyr Asp Gly  
 85 90 95

Pro Val Cys Glu Val Ser Val Thr Pro Lys Thr Val Thr Pro Ala Ser  
 100 105 110

Ser Ala Lys Thr Ser Pro Ala Lys Gln Gln Ala Pro Pro Val Arg Asn  
 115 120 125

Leu His Gln Ser Gly Phe Ser Leu Ser Gly Ala Gln Ile Asp Asp Asn  
 130 135 140

Ile Pro Arg Arg Thr Thr Gln Arg Ile Val Ala Pro Pro Gly Gly Arg  
 145 150 155 160

Ala Asn Ile Thr Ser Leu Gly  
 165

&lt;210&gt; 657

&lt;211&gt; 176

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 657

Xaa Ser Leu Asn Leu Xaa Lys Leu Ala Leu His Arg Gly Gly Gly Arg  
 1 5 10 15

Ser Arg Thr Ser Gly Ser Pro Gly Leu Xaa Glu Phe Gly Thr Ser Ala  
 20 25 30

Val Leu Leu Arg Leu Gly Asp Glu Leu Glu Met Ile Arg Pro Ser Val  
 35 40 45

Tyr Arg Asn Val Ala Arg Gln Leu His Ile Ser Leu Gln Ser Glu Pro  
 50 55 60

Val Val Thr Asp Ala Phe Leu Ala Val Ala Gly His Ile Phe Ser Ala  
 65 70 75 80

Gly Ile Thr Trp Gly Lys Val Val Ser Leu Tyr Ala Val Ala Ala Gly  
 85 90 95

Leu Ala Val Asp Cys Val Arg Gln Ala Gln Pro Ala Met Val His Ala  
 100 105 110

Leu Val Asp Cys Leu Gly Glu Phe Val Arg Lys Thr Leu Ala Thr Trp  
 115 120 125

Leu Arg Arg Arg Gly Gly Trp Thr Asp Val Leu Lys Cys Val Val Ser  
 130 135 140

Thr Asp Pro Gly Leu Arg Ser His Trp Leu Val Ala Ala Leu Cys Ser  
 145 150 155 160

Phe Gly Arg Phe Leu Lys Ala Ala Phe Phe Val Leu Leu Pro Glu Arg  
 165 170 175

&lt;210&gt; 658

&lt;211&gt; 137

&lt;212&gt; PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (75)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (91)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (101)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (124)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (129)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (131)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 658

Gly Pro Val Gly Ser Ser Glu Ala Pro Arg Gly Ala Gly Asp Ala  
1 5 10 15

Gly Met Ala Gly Glu Leu Thr Pro Glu Glu Glu Ala Gln Tyr Lys Lys  
20 25 30

Ala Phe Ser Ala Val Asp Thr Asp Gly Asn Gly Thr Ile Asn Ala Gln  
35 40 45

Glu Leu Gly Ala Ala Leu Lys Ala Thr Gly Lys Asn Leu Ser Glu Ala  
50 55 60

Gln Leu Arg Lys Leu Ile Ser Glu Val Asp Xaa Asp Gly Asp Gly Glu  
65 70 75 80

Ile Ser Phe Gln Glu Phe Leu Thr Ala Ala Xaa Lys Ala Arg Ala Gly  
85 90 95

625

Leu Glu Asp Leu Xaa Val Ala Phe Arg Ala Phe Asp Gln Asp Gly Asp  
                   100                  105                  110

Gly His Ile Thr Val Asp Glu Leu Arg Arg Ala Xaa Ala Gly Leu Gly  
                   115                  120                  125

Xaa Leu Xaa Glu Ile Asp His Phe Gly  
           130                  135

&lt;210&gt; 659

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (28)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 659

Pro Xaa Ser Arg Gln Asp Val Met Asp Ile Val Phe Ile Glu Gln Leu  
       1                  5                  10                  15

Ser Val Ile Thr Thr Ile Gly Val Tyr Asp Trp Xaa Gln Xaa Ser Asn  
                   20                  25                  30

Arg Ser

&lt;210&gt; 660

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 660

Asn Pro Ile Ser Pro Lys Asn Tyr Lys Lys Ile Ser Gln Ala Gln Ser  
       1                  5                  10                  15

626

Gln Leu Pro Val Ile Pro Ala Thr Gln Glu Ala Glu Ser Gly Glu Ser  
                   20                  25                  30

Leu Gly Pro Gly Ala Ala Glu Val Asn Ser Glu Pro Arg Leu His His  
                   35                  40                  45

Arg Thr Pro Ala Trp Ile Thr Lys  
           50                  55

<210> 661  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (29)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (31)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (36)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (39)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 661  
 Tyr Ile Gly Phe Val Ile Leu Val Phe Phe Ala Ser Ser Tyr Val Lys  
       1                  5                  10                  15

Glu Ile Asp Asn Lys Ile Leu Asn Asn Lys Lys Lys Xaa Lys Xaa Ser  
           20                  25                  30

Ser Lys Gly Xaa Val Ala Xaa Ala Ile  
           35                  40

<210> 662  
 <211> 524



627

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (124)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (191)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 662

Cys Glu Ala Trp Arg Gly Arg Ala Asp Pro Gly Gly Gln Ser Cys Leu  
 1 5 10 15

Gln Ala Leu Gln Asn Ser Thr Ala Pro Gln His Pro Gly Leu His Arg  
 20 25 30

Trp Thr Gly Asp Arg Lys Met Pro Pro Arg Arg Asp Arg Gly Cys Asp  
 35 40 45

Pro Val Gly Asn Ile Pro Gln Gly Glu Ser Gly Gly Trp Trp Pro Glu  
 50 55 60

Gly Ala Gly Asp Leu Leu Gly Ala Thr Pro Asp Arg Glu Ser Pro Gln  
 65 70 75 80

Leu Pro Gly Gln Arg Leu Gln Pro His Pro Gln Gln Cys Leu His Gly  
 85 90 95

Arg Arg Val Arg Gly Pro Ser Trp Arg Val Glu Ala Trp Gly Pro Gly  
 100 105 110

Leu His Val Phe Gly Pro Gly Gln Arg Trp Gly Xaa Ser Pro Gln Gly  
 115 120 125

Ile Pro Glu Leu Glu Gln Tyr Asp Pro Pro Glu Leu Ala Asp Ser Ser  
 130 135 140

Gly Arg Val Val Arg Glu Lys Trp Ser Ala Asp Met Trp Arg Leu Gly  
 145 150 155 160

Cys Leu Ile Trp Glu Val Phe Asn Gly Pro Leu Pro Arg Ala Ala Ala  
 165 170 175

Leu Arg Asn Pro Gly Lys Ile Pro Lys Thr Leu Val Pro His Xaa Cys  
 180 185 190

Lys Leu Val Gly Ala Asn Pro Lys Val Arg Pro Asn Pro Ala Arg Phe

628

195	200	205
Leu Gln Asn Cys Arg Ala Pro Gly Gly Phe Met Ser Asn Arg Phe Val 210 215 220		
Glu Thr Asn Leu Phe Leu Glu Glu Ile Gln Ile Lys Glu Pro Ala Glu 225 230 235 240		
Lys Gln Lys Phe Phe Gln Glu Leu Ser Lys Ser Leu Asp Ala Phe Pro 245 250 255		
Glu Asp Phe Cys Arg His Lys Val Leu Pro Gln Leu Leu Thr Ala Phe 260 265 270		
Glu Phe Gly Asn Ala Gly Ala Val Val Leu Thr Pro Leu Phe Lys Val 275 280 285		
Gly Lys Phe Leu Ser Ala Glu Glu Tyr Gln Gln Lys Ile Ile Pro Val 290 295 300		
Val Val Lys Met Phe Ser Ser Thr Asp Arg Ala Met Arg Ile Arg Leu 305 310 315 320		
Leu Gln Gln Met Glu Gln Phe Ile Gln Tyr Leu Asp Glu Pro Thr Val 325 330 335		
Asn Thr Gln Ile Phe Pro His Val Val His Gly Phe Leu Asp Thr Asn 340 345 350		
Pro Ala Ile Arg Glu Gln Thr Val Lys Ser Met Leu Leu Leu Ala Pro 355 360 365		
Lys Leu Asn Glu Ala Asn Leu Asn Val Glu Leu Met Lys His Phe Ala 370 375 380		
Arg Leu Gln Ala Lys Asp Glu Gln Gly Pro Ile Arg Cys Asn Thr Thr 385 390 395 400		
Val Cys Leu Gly Lys Ile Gly Ser Tyr Leu Ser Ala Ser Thr Arg His 405 410 415		
Arg Val Leu Thr Ser Ala Phe Ser Arg Ala Thr Arg Asp Pro Phe Ala 420 425 430		
Pro Ser Arg Val Ala Gly Val Leu Gly Phe Ala Ala Thr His Asn Leu 435 440 445		
Tyr Ser Met Asn Asp Cys Ala Gln Lys Ile Leu Pro Val Leu Cys Gly 450 455 460		
Leu Thr Val Asp Pro Glu Lys Ser Val Arg Asp Gln Ala Phe Lys Ala		

629

465                      470                      475                      480

Phe Gly Ala Ser Cys Pro Asn Trp Ser Leu Cys Arg Arg Thr Arg Pro  
                                  485                      490                      495

Ser Trp Arg Lys Trp Arg Arg Met Ser Met Gln Pro Pro Ala Leu Ala  
                                  500                      505                      510

Trp Glu Glu Pro Gln Leu Ala Gly Gln Ala Gly Pro  
                                  515                      520

<210> 663  
 <211> 272  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (29)  
 <223> Xaa equals any of the naturally occurring L-amino acids\_

<400> 663

Pro Thr Leu Asp Ser Ala Arg Ser Leu Ser Met Arg Ala Pro Ser Leu  
   1                                 5                                 10                                 15

Thr Pro Ser Ala Ala Pro Leu Ser Thr Trp Pro Leu Xaa Ile Leu Val  
                                  20                                 25                                 30

Arg Ser Gly His Asn Arg Ala Val Asp Trp Trp Ser Leu Gly Ala Leu  
                                  35                                 40                                 45

Met Tyr Asp Met Leu Thr Gly Ser Pro Pro Phe Thr Ala Glu Asn Arg  
                                  50                                 55                                 60

Lys Lys Thr Met Asp Lys Ile Ile Arg Gly Lys Leu Ala Leu Pro Pro  
   65                                 70                                 75                                 80

Tyr Leu Thr Pro Asp Ala Arg Asp Leu Val Lys Lys Phe Leu Lys Arg  
                                  85                                 90                                 95

Asn Pro Ser Gln Arg Ile Gly Gly Gly Pro Gly Asp Ala Ala Asp Val  
                                  100                                 105                                 110

Gln Arg His Pro Phe Phe Arg His Met Asn Trp Asp Asp Leu Leu Ala  
                                  115                                 120                                 125

Trp Arg Val Asp Pro Pro Phe Arg Pro Cys Leu Gln Ser Glu Glu Asp  
   130                                 135                                 140

630

Val Ser Gln Phe Asp Thr Arg Phe Thr Arg Gln Thr Pro Val Asp Ser  
 145 150 155 160  
 Pro Asp Asp Thr Ala Leu Ser Glu Ser Ala Asn Gln Ala Phe Leu Gly  
 165 170 175  
 Phe Thr Tyr Val Ala Pro Ser Val Leu Asp Ser Ile Lys Glu Gly Phe  
 180 185 190  
 Ser Phe Gln Pro Lys Leu Arg Ser Pro Arg Arg Leu Asn Ser Ser Pro  
 195 200 205  
 Arg Ala Pro Val Ser Pro Leu Lys Phe Ser Pro Phe Glu Gly Phe Arg  
 210 215 220  
 Pro Ser Pro Ser Leu Pro Glu Pro Thr Glu Leu Pro Leu Pro Pro Leu  
 225 230 235 240  
 Leu Pro Pro Pro Pro Pro Ser Thr Thr Ala Pro Leu Pro Ile Arg Pro  
 245 250 255  
 Pro Ser Gly Thr Lys Lys Ser Lys Arg Gly Arg Gly Arg Pro Gly Arg  
 260 265 270

&lt;210&gt; 664

&lt;211&gt; 256

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (99)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 664

Gly Thr Arg Arg Glu Thr Trp Arg Pro Gly Ser Met Ala Gly Leu Glu  
 1 5 10 15  
 Leu Leu Ser Asp Gln Gly Tyr Arg Val Asp Gly Arg Arg Ala Gly Glu  
 20 25 30  
 Leu Arg Lys Ile Gln Ala Arg Met Gly Val Phe Ala Gln Ala Asp Gly  
 35 40 45  
 Ser Ala Tyr Ile Glu Gln Gly Asn Thr Lys Ala Leu Ala Val Val Tyr  
 50 55 60

631

Gly Pro His Glu Ile Arg Gly Ser Arg Ala Arg Ala Leu Pro Asp Arg  
 65 70 75 80  
 Ala Leu Val Asn Cys Gln Tyr Ser Ser Ala Thr Phe Ser Thr Gly Glu  
 85 90 95  
 Arg Lys Xaa Arg Pro His Gly Asp Arg Lys Ser Cys Glu Met Gly Leu  
 100 105 110  
 Gln Leu Arg Gln Thr Phe Glu Ala Ala Ile Leu Thr Gln Leu His Pro  
 115 120 125  
 Arg Ser Gln Ile Asp Ile Tyr Val Gln Val Leu Gln Ala Asp Gly Gly  
 130 135 140  
 Thr Tyr Ala Ala Cys Val Asn Ala Ala Thr Leu Ala Val Leu Asp Ala  
 145 150 155 160  
 Gly Ile Pro Met Arg Asp Phe Val Cys Ala Cys Ser Ala Gly Phe Val  
 165 170 175  
 Asp Gly Thr Ala Leu Ala Asp Leu Ser His Val Glu Glu Ala Ala Gly  
 180 185 190  
 Gly Pro Gln Leu Ala Leu Ala Leu Leu Pro Ala Ser Gly Gln Ile Ala  
 195 200 205  
 Leu Leu Glu Met Asp Ala Arg Leu His Glu Asp His Leu Glu Arg Val  
 210 215 220  
 Leu Glu Ala Ala Ala Gln Ala Ala Arg Asp Val His Thr Leu Leu Asp  
 225 230 235 240  
 Arg Val Val Arg Gln His Val Arg Glu Ala Ser Ile Leu Leu Gly Asp  
 245 250 255

&lt;210&gt; 665

&lt;211&gt; 241

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (9)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (122)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 665

Pro Arg Gly Asp Lys Ala Arg Thr Xaa Pro Pro Ala Ala Ser Ala Arg  
 1 5 10 15

Pro Ser Arg Ser Lys Arg Gly Gly Glu Glu Arg Val Leu Glu Lys Glu  
 20 25 30

Glu Glu Glu Asp Asp Asp Glu Asp Glu Glu Asp Asp Val Ser  
 35 40 45

Glu Gly Ser Glu Val Pro Glu Ser Asp Arg Pro Ala Gly Ala Gln His  
 50 55 60

His Gln Leu Asn Gly Glu Arg Gly Pro Gln Ser Ala Lys Glu Arg Val  
 65 70 75 80

Lys Glu Trp Thr Pro Cys Gly Pro His Gln Gly Gln Asp Glu Gly Arg  
 85 90 95

Gly Pro Ala Pro Gly Ser Gly Thr Arg Gln Val Phe Ser Met Ala Ala  
 100 105 110

Met Asn Lys Glu Gly Gly Thr Ala Ser Xaa Ala Thr Gly Pro Asp Ser  
 115 120 125

Pro Ser Pro Val Pro Leu Pro Pro Gly Lys Pro Ala Leu Pro Gly Ala  
 130 135 140

Asp Gly Thr Pro Phe Gly Cys Pro Pro Gly Arg Lys Glu Lys Pro Ser  
 145 150 155 160

Asp Pro Val Glu Trp Thr Val Met Asp Val Val Glu Tyr Phe Thr Glu  
 165 170 175

Ala Gly Phe Pro Glu Gln Ala Thr Val Phe Gln Glu Gln Glu Ile Asp  
 180 185 190

Gly Lys Ser Leu Leu Leu Met Gln Arg Thr Asp Val Leu Thr Gly Leu  
 195 200 205

Ser Ile Arg Leu Gly Pro Ala Leu Lys Ile Tyr Glu His His Ile Lys  
 210 215 220

Val Leu Gln Gln Gly His Phe Glu Asp Asp Asp Pro Asp Gly Phe Leu  
 225 230 235 240

633

Gly

&lt;210&gt; 666

&lt;211&gt; 131

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 666

Val Thr Gly Gly Gly Ala Val Val Leu Gly Ala Glu Ser His Ala Ser  
1 5 10 15

Lys Asp Val Ala Ile Asp Met Met Asp Ser Arg Thr Ser Gln Gln Leu  
20 25 30

Gln Leu Ile Asp Glu Gln Asp Ser Tyr Ile Gln Ser Arg Ala Asp Thr  
35 40 45

Met Gln Asn Ile Glu Ser Thr Ile Val Glu Leu Gly Ser Ile Phe Gln  
50 55 60

Gln Leu Ala His Met Val Lys Glu Gln Glu Glu Thr Ile Gln Arg Ile  
65 70 75 80

Asp Glu Asn Val Leu Gly Ala Gln Leu Asp Val Glu Ala Ala His Ser  
85 90 95

Glu Ile Leu Lys Tyr Phe Gln Ser Val Thr Ser Asn Arg Trp Leu Met  
100 105 110

Val Lys Ile Phe Leu Ile Leu Ile Val Phe Phe Ile Ile Phe Val Val  
115 120 125

Phe Leu Ala  
130

&lt;210&gt; 667

&lt;211&gt; 652

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 667

Leu Ser Trp Asn Arg Tyr Thr Ser Val Ser Pro Leu His Arg Ser Leu  
1 5 10 15

Gln Leu Pro Pro Arg Val Ser Gly Val Arg Cys Asp Gln Cys Ala Arg

634

20	25	30
Gly Phe Ser Gly Ile Phe Pro Ala Cys His Pro Cys His Ala Cys Phe		
35	40	45
Gly Asp Trp Asp Arg Val Val Gln Asp Leu Ala Ala Arg Thr Gln Arg		
50	55	60
Leu Glu Gln Arg Ala Gln Glu Leu Gln Gln Thr Gly Val Leu Gly Ala		
65	70	75
Phe Glu Ser Ser Phe Trp His Met Gln Glu Lys Leu Gly Ile Val Gln		
85	90	95
Gly Ile Val Gly Ala Arg Asn Thr Ser Ala Ala Ser Thr Ala Gln Leu		
100	105	110
Val Glu Ala Thr Glu Glu Leu Arg Arg Glu Ile Gly Glu Ala Thr Glu		
115	120	125
His Leu Thr Gln Leu Glu Ala Asp Leu Thr Asp Val Gln Asp Glu Asn		
130	135	140
Phe Asn Ala Asn His Ala Leu Ser Gly Leu Glu Arg Asp Arg Leu Ala		
145	150	155
Leu Asn Leu Thr Leu Arg Gln Leu Asp Gln His Leu Asp Leu Leu Lys		
165	170	175
His Ser Asn Phe Leu Gly Ala Tyr Asp Ser Ile Arg His Ala His Ser		
180	185	190
Gln Ser Ala Glu Ala Glu Arg Arg Ala Asn Thr Ser Ala Leu Ala Val		
195	200	205
Pro Ser Pro Val Ser Asn Ser Ala Ser Ala Arg His Arg Thr Glu Ala		
210	215	220
Leu Met Asp Ala Gln Lys Glu Asp Phe Asn Ser Lys His Met Ala Asn		
225	230	235
Gln Arg Ala Leu Gly Lys Leu Ser Ala His Thr His Thr Leu Ser Leu		
245	250	255
Thr Asp Ile Asn Glu Leu Val Cys Gly Ala Pro Gly Asp Ala Pro Cys		
260	265	270
Ala Thr Ser Pro Cys Gly Gly Ala Gly Cys Arg Asp Glu Asp Gly Gln		
275	280	285
Pro Arg Cys Gly Gly Leu Ser Cys Asn Gly Ala Ala Ala Thr Ala Asp		



635

290	295	300
Leu Ala Leu Gly Arg Ala Arg His Thr Gln Ala Glu Leu Gln Arg Ala		
305	310	315 320
Leu Ala Glu Gly Gly Ser Ile Leu Ser Arg Val Ala Glu Thr Arg Arg		
	325	330 335
Gln Ala Ser Glu Ala Gln Gln Arg Ala Gln Ala Ala Leu Asp Lys Ala		
	340	345 350
Asn Ala Ser Arg Gly Gln Val Glu Gln Ala Asn Gln Glu Leu Gln Glu		
	355	360 365
Leu Ile Gln Ser Val Lys Asp Phe Leu Asn Gln Glu Gly Ala Asp Pro		
	370	375 380
Asp Ser Ile Glu Met Val Ala Thr Arg Val Leu Glu Leu Ser Ile Pro		
	385	390 395 400
Ala Ser Ala Glu Gln Ile Gln His Leu Ala Gly Ala Ile Ala Glu Arg		
	405	410 415
Val Arg Ser Leu Ala Asp Val Asp Ala Ile Leu Ala Arg Thr Val Gly		
	420	425 430
Asp Val Arg Arg Ala Glu Gln Leu Leu Gln Asp Ala Arg Arg Ala Arg		
	435	440 445
Ser Trp Ala Glu Asp Glu Lys Gln Lys Ala Glu Thr Val Gln Ala Ala		
	450	455 460
Leu Glu Glu Ala Gln Arg Ala Gln Gly Ile Ala Gln Gly Ala Ile Arg		
	465	470 475 480
Gly Ala Val Ala Asp Thr Arg Asp Thr Glu Gln Thr Leu Tyr Gln Val		
	485	490 495
Gln Glu Arg Met Ala Gly Ala Glu Arg Ala Leu Ser Ser Ala Gly Glu		
	500	505 510
Arg Ala Arg Gln Leu Asp Ala Leu Leu Glu Ala Leu Lys Leu Lys Arg		
	515	520 525
Ala Gly Asn Ser Leu Ala Ala Ser Thr Ala Glu Glu Thr Ala Gly Ser		
	530	535 540
Ala Gln Gly Arg Ala Gln Glu Ala Glu Gln Leu Leu Arg Gly Pro Leu		
	545	550 555 560
Gly Asp Gln Tyr Gln Thr Val Lys Ala Leu Ala Glu Arg Lys Ala Gln		

565										570					575				
Gly	Val	Leu	Ala	Ala	Gln	Ala	Arg	Ala	Glu	Gln	Leu	Arg	Asp	Glu	Ala				
580								585					590						
Arg	Asp	Leu	Leu	Gln	Ala	Ala	Gln	Asp	Lys	Leu	Gln	Arg	Leu	Gln	Glu				
595				600					605										
Leu	Glu	Gly	Thr	Tyr	Glu	Glu	Asn	Glu	Arg	Ala	Leu	Glu	Ser	Lys	Ala				
610				615					620										
Ala	Gln	Leu	Asp	Gly	Leu	Glu	Ala	Arg	Met	Arg	Ser	Val	Leu	Gln	Ala				
625			630					635							640				
Ile	Asn	Leu	Gln	Val	Gln	Ile	Tyr	Asn	Thr	Cys	Gln								
645							650												

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<210> 668
<211> 406
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (84)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```

<400> 668
Gly Ala Val Arg Ser Ser Cys Ala Glu Leu Gln Ala Arg Val Met Ala
  1                      5                      10                      15

Ala Leu Arg Gln Pro Gln Val Ala Glu Cys Trp Pro Arg Pro Gly Glu
      20                      25                      30

Pro Ser Gly Arg Ser Ser Gly Pro Ser Pro Ser Trp Pro Cys Gln Arg
      35                      40                      45

Arg Ala Ala Cys Asn Leu Ile Gly Glu His Thr Asp Tyr Asn Gln Gly
      50                      55                      60

Leu Val Leu Pro Met Ala Leu Glu Leu Met Thr Val Leu Val Gly Ser
      65                      70                      75                      80

Pro Arg Lys Xaa Gly Leu Val Ser Leu Leu Thr Thr Ser Glu Gly Ala
      85                      90                      95

Asp Glu Pro Gln Arg Leu Gln Phe Pro Leu Pro Thr Ala Gln Arg Ser
      100                      105                      110

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Leu Glu Pro Gly Thr Pro Arg Trp Ala Asn Tyr Val Lys Gly Val Ile  
115 120 125

Gln Tyr Tyr Pro Ala Ala Pro Leu Pro Gly Phe Ser Ala Val Val Val  
130 135 140

Ser Ser Val Pro Leu Gly Gly Gly Leu Ser Ser Ser Ala Ser Leu Glu  
145 150 155 160

Val Ala Thr Tyr Thr Phe Leu Gln Gln Leu Cys Pro Asp Ser Gly Thr  
165 170 175

Ile Ala Ala Arg Ala Gln Val Cys Gln Gln Ala Glu His Ser Phe Ala  
180 185 190

Gly Met Pro Cys Gly Ile Met Asp Gln Phe Ile Ser Leu Met Gly Gln  
195 200 205

Lys Gly His Ala Leu Leu Ile Asp Cys Arg Ser Leu Glu Thr Ser Leu  
210 215 220

Val Pro Leu Ser Asp Pro Lys Leu Ala Val Leu Ile Thr Asn Ser Asn  
225 230 235 240

Val Arg His Ser Leu Ala Ser Ser Glu Tyr Pro Val Arg Arg Arg Gln  
245 250 255

Cys Glu Glu Val Ala Arg Ala Leu Gly Lys Glu Ser Leu Arg Glu Val  
260 265 270

Gln Leu Glu Glu Leu Glu Ala Ala Arg Asp Leu Val Ser Lys Glu Gly  
275 280 285

Phe Arg Arg Ala Arg His Val Val Gly Glu Ile Arg Arg Thr Ala Gln  
290 295 300

Ala Ala Ala Ala Leu Arg Arg Gly Asp Tyr Arg Ala Phe Gly Arg Leu  
305 310 315 320

Met Val Glu Ser His Arg Ser Leu Arg Asp Asp Tyr Glu Val Ser Cys  
325 330 335

Pro Glu Leu Asp Gln Leu Val Glu Ala Ala Leu Ala Val Pro Gly Val  
340 345 350

Tyr Gly Ser Arg Met Thr Gly Gly Gly Phe Gly Gly Cys Thr Val Thr  
355 360 365

Leu Leu Glu Ala Ser Ala Ala Pro His Ala Met Arg His Ile Gln Glu  
370 375 380

638

His Tyr Gly Gly Thr Ala Thr Phe Tyr Leu Ser Gln Ala Ala Asp Gly  
 385 390 395 400

Ala Lys Val Leu Cys Leu  
 405

&lt;210&gt; 669

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 669

Pro Glu Pro Thr Val Val Met Ala Ala Arg Ala Leu Cys Met Leu Gly  
 1 5 10 15

Leu Val Leu Ala Leu Leu Ser Ser Ser Ala Glu Glu Tyr Val Gly  
 20 25 30

Leu Ser Ala Asn Gln Cys Ala Val Pro Ala Lys Asp Arg Val Asp Cys  
 35 40 45

Gly Tyr Pro His Val Thr Pro Lys Glu Cys Asn Asn Arg Gly Cys Cys  
 50 55 60

Phe Asp Ser Arg Ile Pro Gly Val Pro Trp Cys Phe Lys Pro Leu Gln  
 65 70 75 80

Glu Ala Glu Cys Thr Phe  
 85

&lt;210&gt; 670

&lt;211&gt; 392

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 670

Gly Gly Gly Ala Arg Xaa Ser Pro Ala Thr Gln Pro Pro Pro Leu Leu  
 1 5 10 15

Pro Pro Ser Ala Thr Gly Pro Asp Ala Thr Val Gly Gly Pro Ala Pro  
 20 25 30

Thr Pro Leu Leu Pro Pro Ser Ala Thr Ala Ser Val Lys Met Glu Pro  
 35 40 45  
 Glu Asn Lys Tyr Leu Pro Glu Leu Met Ala Glu Lys Asp Ser Leu Asp  
 50 55 60  
 Pro Ser Phe Thr His Ala Met Gln Leu Leu Thr Ala Glu Ile Glu Lys  
 65 70 75 80  
 Ile Gln Lys Gly Asp Ser Lys Lys Asp Asp Glu Glu Asn Tyr Leu Asp  
 85 90 95  
 Leu Phe Ser His Lys Asn Met Lys Leu Lys Glu Arg Val Leu Ile Pro  
 100 105 110  
 Val Lys Gln Tyr Pro Lys Phe Asn Phe Val Gly Lys Ile Leu Gly Pro  
 115 120 125  
 Gln Gly Asn Thr Ile Lys Arg Leu Gln Glu Glu Thr Gly Ala Lys Ile  
 130 135 140  
 Ser Val Leu Gly Lys Gly Ser Met Arg Asp Lys Ala Lys Glu Glu Glu  
 145 150 155 160  
 Leu Arg Lys Gly Gly Asp Pro Lys Tyr Ala His Leu Asn Met Asp Leu  
 165 170 175  
 His Val Phe Ile Glu Val Phe Gly Pro Pro Cys Glu Ala Tyr Ala Leu  
 180 185 190  
 Met Ala His Ala Met Glu Glu Val Lys Lys Phe Leu Val Pro Asp Met  
 195 200 205  
 Met Asp Asp Ile Cys Gln Glu Gln Phe Leu Glu Leu Ser Tyr Leu Asn  
 210 215 220  
 Gly Val Pro Glu Pro Ser Arg Gly Arg Gly Val Pro Val Arg Gly Arg  
 225 230 235 240  
 Gly Ala Ala Pro Pro Pro Pro Pro Val Pro Arg Gly Arg Gly Val Gly  
 245 250 255  
 Pro Pro Arg Gly Ala Leu Val Arg Gly Thr Pro Val Arg Gly Ala Ile  
 260 265 270  
 Thr Arg Gly Ala Thr Val Thr Arg Gly Val Pro Pro Pro Pro Thr Val  
 275 280 285  
 Arg Gly Ala Pro Ala Pro Arg Ala Arg Thr Ala Gly Ile Gln Arg Ile  
 290 295 300

640

Pro Leu Pro Pro Pro Pro Ala Pro Glu Thr Tyr Glu Glu Tyr Gly Tyr  
305 310 315 320

Asp Asp Thr Tyr Ala Glu Gln Ser Tyr Glu Gly Tyr Glu Gly Tyr Tyr  
325 330 335

Ser Gln Ser Gln Gly Asp Ser Glu Tyr Tyr Asp Tyr Gly His Gly Glu  
340 345 350

Val Gln Asp Ser Tyr Glu Ala Tyr Gly Gln Asp Asp Trp Asn Gly Thr  
355 360 365

Arg Pro Ser Leu Lys Ala Pro Pro Ala Arg Pro Val Lys Gly Ala Tyr  
370 375 380

Arg Glu His Pro Tyr Gly Arg Tyr  
385 390

&lt;210&gt; 671

&lt;211&gt; 180

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 671

Arg Asn Met Ser Ser Phe Ser Arg Ala Pro Gln Gln Trp Ala Thr Phe  
1 5 10 15

Ala Arg Ile Trp Tyr Leu Leu Asp Gly Lys Met Gln Pro Pro Gly Lys  
20 25 30

Leu Ala Ala Met Ala Ser Ile Arg Leu Gln Gly Leu His Lys Pro Val  
35 40 45

Tyr His Ala Leu Ser Asp Cys Gly Asp His Val Val Ile Met Asn Thr  
50 55 60

Arg His Ile Ala Phe Ser Gly Asn Lys Trp Glu Gln Lys Val Tyr Ser  
65 70 75 80

Ser His Thr Gly Tyr Pro Gly Gly Phe Arg Gln Val Thr Ala Ala Gln  
85 90 95

Leu His Leu Arg Asp Pro Val Ala Ile Val Lys Leu Ala Ile Tyr Gly  
100 105 110

Met Leu Pro Lys Asn Leu His Arg Arg Thr Met Met Glu Arg Leu His  
115 120 125

Leu Phe Pro Asp Glu Tyr Ile Pro Glu Asp Ile Leu Lys Asn Leu Val

641

130 135 140  
Glu Glu Leu Pro Gln Pro Arg Lys Ile Pro Lys Arg Leu Asp Glu Tyr  
145 150 155 160  
Thr Gln Glu Glu Ile Asp Ala Phe Pro Arg Leu Trp Thr Pro Pro Glu  
165 170 175  
Asp Tyr Arg Leu  
180

<210> 672  
<211> 78  
<212> PRT  
<213> Homo sapiens

<400> 672  
Glu Asn Tyr Gln Phe Thr Tyr Arg Arg Phe Phe Phe Pro Asn Ser Arg  
1 5 10 15  
Phe His Pro Arg Pro Phe Glu Glu Leu Gln Thr Leu Ser Leu Arg Lys  
20 25 30  
Glu Arg Gly Gln Pro Lys Ile Asn Ala Lys Phe Ala Tyr Thr Pro Ser  
35 40 45  
His Ser Asp Val Leu Val Val Thr Tyr Tyr Gln Cys Gly Arg Glu Pro  
50 55 60  
Lys Leu His Phe Arg Ser Lys Tyr Ser Leu Cys Arg Tyr Cys  
65 70 75

<210> 673  
<211> 139  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (113)  
<223> Xaa equals any of the naturally occurring L-amino acids  
  
<220>  
<221> SITE  
<222> (132)  
<223> Xaa equals any of the naturally occurring L-amino acids

642

&lt;400&gt; 673

Pro Thr Arg Pro Pro Leu Cys Arg Gly Ala Ala Ser Arg Gly Leu Leu  
1 5 10 15

Cys Lys Trp Ala Pro Trp Pro Ser Ala Pro Val Pro Ala Thr Arg Asp  
20 25 30

Arg Ala Pro Arg Pro Ala Arg Gly Arg Arg Pro Gly Arg Leu Gly Ser  
35 40 45

Thr Ser Ser Asn Ser Ser Cys Ser Ser Thr Glu Cys Pro Gly Glu Ala  
50 55 60

Ile Pro His Pro Pro Gly Leu Pro Lys Ala Asp Pro Gly His Trp Trp  
65 70 75 80

Ala Ser Phe Phe Phe Gly Lys Ser Thr Leu Pro Phe Met Ala Thr Val  
85 90 95

Leu Glu Ser Ala Glu His Ser Glu Pro Pro Gln Ala Ser Ser Ser Met  
100 105 110

Xaa Ala Cys Gly Leu Ala Arg Glu Ala Pro Arg Lys Gln Pro Gly Gly  
115 120 125

Gln Ser Ser Xaa Ala Ser Ala Gly Pro Pro Ser  
130 135

&lt;210&gt; 674

&lt;211&gt; 279

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (193)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 674



643

Glu Arg Ala His Ser Leu Xaa His Gly Val Asp Gly Glu Pro Cys Pro  
 1 5 10 15  
 Glu Asp Tyr Lys Tyr Ile Ser Glu Asn Cys Glu Thr Ser Thr Met Asn  
 20 25 30  
 Ile Asp Arg Asn Ile Thr His Leu Gln His Cys Thr Phe Val Asp Asp  
 35 40 45  
 Cys Ser Ser Ser Asn Cys Leu Cys Gly Xaa Phe Ser Ile Arg Cys Trp  
 50 55 60  
 Tyr Asp Lys Asp Gly Arg Leu Leu Gln Glu Phe Asn Lys Ile Glu Pro  
 65 70 75 80  
 Pro Leu Ile Phe Glu Cys Asn Gln Ala Cys Ser Cys Trp Arg Asn Cys  
 85 90 95  
 Lys Asn Arg Val Val Gln Ser Gly Ile Lys Val Arg Leu Gln Leu Tyr  
 100 105 110  
 Arg Thr Ala Lys Met Gly Trp Gly Val Arg Ala Leu Gln Thr Ile Pro  
 115 120 125  
 Gln Gly Thr Phe Ile Cys Glu Tyr Val Gly Glu Leu Ile Ser Asp Ala  
 130 135 140  
 Glu Ala Asp Val Arg Glu Asp Asp Ser Tyr Leu Phe Asp Leu Asp Asn  
 145 150 155 160  
 Lys Asp Gly Glu Val Tyr Cys Ile Asp Ala Arg Tyr Tyr Gly Asn Ile  
 165 170 175  
 Ser Arg Phe Ile Asn His Leu Cys Asp Pro Asn Ile Ile Pro Val Arg  
 180 185 190  
 Xaa Phe Met Leu His Gln Asp Leu Arg Phe Pro Arg Ile Ala Phe Phe  
 195 200 205  
 Ser Ser Arg Asp Ile Arg Thr Gly Glu Glu Leu Gly Phe Asp Tyr Gly  
 210 215 220  
 Asp Arg Phe Trp Asp Ile Lys Ser Lys Tyr Phe Thr Cys Gln Cys Gly  
 225 230 235 240  
 Ser Glu Lys Cys Lys His Ser Ala Glu Ala Ile Ala Leu Glu Gln Ser  
 245 250 255  
 Arg Leu Ala Arg Leu Asp Pro His Pro Glu Leu Leu Pro Glu Leu Gly  
 260 265 270

644

Ser Leu Pro Pro Val Asn Thr  
275

<210> 675  
<211> 405  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (393)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (394)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 675  
Arg Asn Thr Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu  
1 5 10 15  
Glu Ala Ser Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys  
20 25 30  
Lys Tyr Ser Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys  
35 40 45  
Thr Glu Thr Val Glu Glu Pro Met Glu Glu Glu Glu Ala Ala Lys Glu  
50 55 60  
Glu Lys Glu Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu  
65 70 75 80  
Glu Lys Lys Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp  
85 90 95  
Glu Leu Met Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu  
100 105 110  
Val Glu Glu Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu  
115 120 125  
Ser Asp Asp Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val  
130 135 140  
Thr Phe Lys Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu  
145 150 155 160

645

Phe Asp Glu Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val  
 165 170 175  
 Arg Arg Val Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr  
 180 185 190  
 Leu Asn Phe Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn  
 195 200 205  
 Val Ser Arg Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg  
 210 215 220  
 Lys Lys Leu Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp  
 225 230 235 240  
 Asp Lys Tyr Asn Asp Thr Phe Trp Lys Glu Phe Gly Thr Asn Ile Lys  
 245 250 255  
 Leu Gly Val Ile Glu Asp His Ser Asn Arg Thr Arg Leu Ala Lys Leu  
 260 265 270  
 Leu Arg Phe Gln Ser Ser His His Pro Thr Asp Ile Thr Ser Leu Asp  
 275 280 285  
 Gln Tyr Val Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met  
 290 295 300  
 Ala Gly Ser Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg  
 305 310 315 320  
 Leu Leu Lys Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp  
 325 330 335  
 Glu Tyr Cys Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln  
 340 345 350  
 Asn Val Ala Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys  
 355 360 365  
 Glu Ser Arg Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp  
 370 375 380  
 Met Lys Asp Lys Ala Leu Lys Gly Xaa Xaa Leu Trp Glu Ile Leu Pro  
 385 390 395 400  
 Ile Cys Gly Lys Tyr  
 405

&lt;210&gt; 676

646

&lt;211&gt; 465

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (5)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (6)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (16)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 676

Asn Asp Ser Leu Xaa Xaa Lys Ala Gly Thr Pro Ala Gly Asn Arg Xaa  
1 5 10 15

Gly Ile Pro Gly Ser Thr His Ala Ser Ala Ala Ala Pro Phe Ala Ala  
20 25 30

Ala Leu Ala Arg Asp Pro Asn Pro Ala Ser Pro Leu Pro Glu His Arg  
35 40 45

Pro Arg Leu His Arg Gly Pro Gly Pro Pro Ala Arg Leu Ala Ala Ala  
50 55 60

Met Ala Asp Pro Lys Tyr Ala Asp Leu Pro Gly Ile Ala Arg Asn Glu  
65 70 75 80

Pro Asp Val Tyr Glu Thr Ser Asp Leu Pro Glu Asp Asp Gln Ala Glu  
85 90 95

Phe Asp Ala Glu Glu Leu Thr Ser Thr Ser Val Glu His Ile Ile Val  
100 105 110

Asn Pro Asn Ala Ala Tyr Asp Lys Phe Lys Asp Lys Arg Val Gly Thr  
115 120 125

Lys Gly Leu Asp Phe Ser Asp Arg Ile Gly Lys Thr Lys Arg Thr Gly  
130 135 140

Tyr Glu Ser Gly Glu Tyr Glu Met Leu Gly Glu Gly Leu Gly Val Lys  
145 150 155 160

Glu Thr Pro Gln Gln Lys Tyr Gln Arg Leu Leu His Glu Val Gln Glu

647

165	170	175
Leu Thr Thr Glu Val Glu Lys Ile Lys Thr Thr Val Lys Glu Ser Ala		
180	185	190
Thr Glu Glu Lys Leu Thr Pro Val Leu Leu Ala Lys Gln Leu Ala Ala		
195	200	205
Leu Lys Gln Gln Leu Val Ala Ser His Leu Glu Lys Leu Leu Gly Pro		
210	215	220
Asp Ala Ala Ile Asn Leu Thr Asp Pro Asp Gly Ala Leu Ala Lys Arg		
225	230	235
Leu Leu Leu Gln Leu Glu Ala Thr Lys Asn Ser Lys Gly Gly Ser Gly		
245	250	255
Gly Lys Thr Thr Gly Thr Pro Pro Asp Ser Ser Leu Val Thr Tyr Glu		
260	265	270
Leu His Ser Arg Pro Glu Gln Asp Lys Phe Ser Gln Ala Ala Lys Val		
275	280	285
Ala Glu Leu Glu Lys Arg Leu Thr Glu Leu Glu Thr Ala Val Arg Cys		
290	295	300
Asp Gln Asp Ala Gln Asn Pro Leu Ser Ala Gly Leu Gln Gly Ala Cys		
305	310	315
Leu Met Glu Thr Val Glu Leu Leu Gln Ala Lys Val Ser Ala Leu Asp		
325	330	335
Leu Ala Val Leu Asp Gln Val Glu Ala Arg Leu Gln Ser Val Leu Gly		
340	345	350
Lys Val Asn Glu Ile Ala Lys His Lys Ala Ser Val Glu Asp Ala Asp		
355	360	365
Thr Gln Ser Lys Val His Gln Leu Tyr Glu Thr Ile Gln Arg Trp Ser		
370	375	380
Pro Ile Ala Ser Thr Leu Pro Glu Leu Val Gln Arg Leu Val Thr Ile		
385	390	395
Lys Gln Leu His Glu Gln Ala Met Gln Phe Gly Gln Leu Leu Thr His		
405	410	415
Leu Asp Thr Thr Gln Gln Met Ile Ala Asn Ser Leu Lys Asp Asn Thr		
420	425	430
Thr Leu Leu Thr Gln Val Gln Thr Thr Met Arg Glu Asn Leu Ala Thr		

648

435                      440                      445  
 Val Glu Gly Asn Phe Ala Ser Ile Asp Glu Arg Met Lys Lys Leu Gly  
 450                      455                      460

Lys  
 465

<210> 677  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<400> 677  
 Ser Ser Phe Leu Asn Ser Asp Leu Gly Leu Ser Leu Ala Arg Asn Leu  
 1                      5                      10                      15  
 Ala Phe Ser Phe Thr Thr Lys Glu Arg Asp Gln Lys Pro Leu Ile Phe  
 20                      25                      30  
 Asn Phe His Lys Met Leu Glu Val Tyr Ile Tyr Ile Tyr Ile Phe Leu  
 35                      40                      45

<210> 678  
 <211> 940  
 <212> PRT  
 <213> Homo sapiens

<400> 678  
 Val Leu Gly Glu Gly Ile Ser Phe Leu Leu Ser Pro Pro Leu Pro Thr  
 1                      5                      10                      15  
 Pro Ser Ile Asn Ile Ile Leu Leu Lys Ile Leu Arg Cys Gln Ala Ala  
 20                      25                      30  
 Lys Val Glu Ser Ala Ile Ala Glu Gly Gly Ala Ser Arg Phe Ser Ala  
 35                      40                      45  
 Ser Ser Gly Gly Gly Gly Ser Arg Gly Ala Pro Gln His Tyr Pro Lys  
 50                      55                      60  
 Thr Ala Gly Asn Ser Glu Phe Leu Gly Lys Thr Pro Gly Gln Asn Ala  
 65                      70                      75                      80



650

Pro Lys Thr Ile Asn Gln Ile Arg Gln Asp Ala Val Lys Asp Leu Gly  
 355 360 365  
 Val Phe Ile Pro Ala Pro Met Ala Gln Gly Met Arg Ser Asp Phe Phe  
 370 375 380  
 Leu Glu Gly Pro Phe Met Pro Pro Arg Met Lys Met Asp Arg Asp Pro  
 385 390 395 400  
 Leu Gly Gly Leu Ala Asp Met Phe Gly Gln Met Pro Gly Ser Gly Ile  
 405 410 415  
 Gly Thr Gly Pro Gly Val Ile Gln Asp Arg Phe Ser Pro Thr Met Gly  
 420 425 430  
 Arg His Arg Ser Asn Gln Leu Phe Asn Gly His Gly Gly His Ile Met  
 435 440 445  
 Pro Pro Thr Gln Ser Gln Phe Gly Glu Met Gly Gly Lys Phe Met Lys  
 450 455 460  
 Ser Gln Gly Leu Ser Gln Leu Tyr His Asn Gln Ser Gln Gly Leu Leu  
 465 470 475 480  
 Ser Gln Leu Gln Gly Gln Ser Lys Asp Met Pro Pro Arg Phe Ser Lys  
 485 490 495  
 Lys Gly Gln Leu Asn Ala Asp Glu Ile Ser Leu Arg Pro Ala Gln Ser  
 500 505 510  
 Phe Leu Met Asn Lys Asn Gln Val Pro Lys Leu Gln Pro Gln Ile Thr  
 515 520 525  
 Met Ile Pro Pro Ser Ala Gln Pro Pro Arg Thr Gln Thr Pro Pro Leu  
 530 535 540  
 Gly Gln Thr Pro Gln Leu Gly Leu Lys Thr Asn Pro Pro Leu Ile Gln  
 545 550 555 560  
 Glu Lys Pro Ala Lys Thr Ser Lys Lys Pro Pro Pro Ser Lys Glu Glu  
 565 570 575  
 Leu Leu Lys Leu Thr Glu Thr Val Val Thr Glu Tyr Leu Asn Ser Gly  
 580 585 590  
 Asn Ala Asn Glu Ala Val Asn Gly Val Arg Glu Met Arg Ala Pro Lys  
 595 600 605  
 His Phe Leu Pro Glu Met Leu Ser Lys Val Ile Ile Leu Ser Leu Asp  
 610 615 620



651

Arg Ser Asp Glu Asp Lys Glu Lys Ala Ser Ser Leu Ile Ser Leu Leu  
 625 630 635 640  
 Lys Gln Glu Gly Ile Ala Thr Ser Asp Asn Phe Met Gln Ala Phe Leu  
 645 650 655  
 Asn Val Leu Asp Gln Cys Pro Lys Leu Glu Val Asp Ile Pro Leu Val  
 660 665 670  
 Lys Ser Tyr Leu Ala Gln Phe Ala Ala Arg Ala Ile Ile Ser Glu Leu  
 675 680 685  
 Val Ser Ile Ser Glu Leu Ala Gln Pro Leu Glu Ser Gly Thr His Phe  
 690 695 700  
 Pro Leu Phe Leu Leu Cys Leu Gln Gln Leu Ala Lys Leu Gln Asp Arg  
 705 710 715 720  
 Glu Trp Leu Thr Glu Leu Phe Gln Gln Ser Lys Val Asn Met Gln Lys  
 725 730 735  
 Met Leu Pro Glu Ile Asp Gln Asn Lys Asp Arg Met Leu Glu Ile Leu  
 740 745 750  
 Glu Gly Lys Gly Leu Ser Phe Leu Phe Pro Leu Leu Lys Leu Glu Lys  
 755 760 765  
 Glu Leu Leu Lys Gln Ile Lys Leu Asp Pro Ser Pro Gln Thr Ile Tyr  
 770 775 780  
 Lys Trp Ile Lys Asp Asn Ile Ser Pro Lys Leu His Val Asp Lys Gly  
 785 790 795 800  
 Phe Val Asn Ile Leu Met Thr Ser Phe Leu Gln Tyr Ile Ser Ser Glu  
 805 810 815  
 Val Asn Pro Pro Ser Asp Glu Thr Asp Ser Ser Ser Ala Pro Ser Lys  
 820 825 830  
 Glu Gln Leu Glu Gln Glu Lys Gln Leu Leu Leu Ser Phe Lys Pro Val  
 835 840 845  
 Met Gln Lys Phe Leu His Asp His Val Asp Leu Gln Val Ser Ala Leu  
 850 855 860  
 Tyr Ala Leu Gln Val His Cys Tyr Asn Ser Asn Phe Pro Lys Gly Met  
 865 870 875 880  
 Leu Leu Arg Phe Phe Val His Phe Tyr Asp Met Glu Ile Ile Glu Glu  
 885 890 895

652

Glu Ala Phe Leu Ala Trp Lys Glu Asp Ile Thr Gln Glu Phe Pro Gly  
                   900                  905                  910

Lys Gly Lys Ala Leu Phe Gln Val Asn Gln Trp Leu Thr Trp Leu Glu  
           915                  .          920                  925

Thr Ala Glu Glu Glu Glu Ser Glu Glu Glu Ala Asp  
       930                  935                  940

&lt;210&gt; 679

&lt;211&gt; 212

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (7)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (160)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (172)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 679

Ser Trp Lys Glu Glu Glu Xaa Lys Pro His Leu Gln Gly Lys Pro Gly  
   1                  5                  10                  15

Arg Pro Leu Ser Pro Ala Asn Val Pro Ala Leu Pro Gly Glu Thr Val  
           20                  25                  30

Thr Ser Pro Val Arg Leu His Pro Asp Tyr Leu Ser Pro Glu Glu Ile  
       35                  40                  45

Gln Arg Gln Leu Gln Asp Ile Glu Arg Arg Leu Asp Ala Leu Glu Leu  
       50                  55                  60

Arg Gly Val Glu Leu Glu Lys Arg Leu Arg Ala Ala Glu Gly Asp Asp  
       65                  70                  75                  80

Ala Glu Asp Ser Leu Met Val Asp Trp Phe Trp Leu Ile His Glu Lys  
           85                  90                  95

Gln Leu Leu Leu Arg Gln Glu Ser Glu Leu Met Tyr Lys Ser Lys Ala

653

100 105 110  
Gln Arg Leu Glu Glu Gln Gln Leu Asp Ile Glu Gly Glu Leu Arg Arg  
115 120 125  
Leu Met Ala Lys Pro Glu Ala Leu Lys Ser Leu Gln Glu Arg Arg Arg  
130 135 140  
Glu Gln Glu Leu Leu Glu Gln Tyr Val Ser Thr Val Asn Asp Arg Xaa  
145 150 155 160  
Asp Ile Val Asp Ser Leu Asp Glu Asp Arg Leu Xaa Glu Gln Glu Glu  
165 170 175  
Asp Gln Met Leu Arg Asp Met Ile Glu Lys Leu Gly Leu Gln Arg Lys  
180 185 190  
Lys Ser Lys Phe Arg Leu Ser Lys Ile Trp Ser Pro Lys Ser Lys Ser  
195 200 205  
Ser Pro Ser Gln  
210

<210> 680  
<211> 412  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (172)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (404)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 680  
Val Ala Val Glu Leu Gly Ser Leu Arg Gly Gly Thr Met Ala Ser Glu  
1 5 10 15  
Lys Pro Leu Ala Ala Val Thr Cys Thr Ala Pro Val Asn Ile Ala Val  
20 25 30  
Ile Lys Tyr Trp Gly Lys Arg Asp Glu Glu Leu Val Leu Pro Ile Asn  
35 40 45  
Ser Ser Leu Ser Val Thr Leu His Gln Asp Gln Leu Lys Thr Thr Thr

654

50	55	60
Thr Ala Val Ile Ser Lys Asp Phe Thr Glu Asp Arg Ile Trp Leu Asn		
65	70	75 80
Gly Arg Glu Glu Asp Val Gly Gln Pro Arg Leu Gln Ala Cys Leu Arg		
	85	90 95
Glu Ile Arg Cys Leu Ala Arg Lys Arg Arg Asn Ser Arg Asp Gly Asp		
	100	105 110
Pro Leu Pro Ser Ser Leu Ser Cys Lys Val His Val Ala Ser Val Asn		
	115	120 125
Asn Phe Pro Thr Ala Ala Gly Leu Ala Ser Ser Ala Ala Gly Tyr Ala		
	130	135 140
Cys Leu Ala Tyr Thr Leu Ala Arg Val Tyr Gly Val Glu Ser Asp Leu		
	145	150 155 160
Ser Glu Val Ala Arg Arg Gly Ser Gly Ser Ala Xaa Arg Ser Leu Tyr		
	165	170 175
Gly Gly Phe Val Glu Trp Gln Met Gly Glu Gln Ala Asp Gly Lys Asp		
	180	185 190
Ser Ile Ala Arg Gln Val Ala Pro Glu Ser His Trp Pro Glu Leu Arg		
	195	200 205
Val Leu Ile Leu Val Val Ser Ala Glu Lys Lys Leu Thr Gly Ser Thr		
	210	215 220
Val Gly Met Arg Ala Ser Val Glu Thr Ser Pro Leu Leu Arg Phe Arg		
	225	230 235 240
Ala Glu Ser Val Val Pro Ala Arg Met Ala Glu Met Ala Arg Cys Ile		
	245	250 255
Arg Glu Arg Asp Phe Pro Ser Phe Ala Gln Leu Thr Met Lys Asp Ser		
	260	265 270
Asn Gln Phe His Ala Thr Cys Leu Asp Thr Phe Pro Pro Ile Ser Tyr		
	275	280 285
Leu Asn Ala Ile Ser Trp Arg Ile Ile His Leu Val His Arg Phe Asn		
	290	295 300
Ala His His Gly Asp Thr Lys Val Ala Tyr Thr Phe Asp Ala Gly Pro		
	305	310 315 320
Asn Ala Val Ile Phe Thr Leu Asp Asp Thr Val Ala Glu Phe Val Ala		

325

330

335

Leu Leu Gly Xaa Asp Gly Leu Pro Lys Pro Ala Ala  
405 410

<213> Homo sapiens

Pro Arg Glu Arg Asn Cys Ala Pro Ser Val Leu Leu Pro  
50 55 60

<213> Homo sapiens

Gln Arg Pro Pro Pro Gln Ser Pro Thr Ala Thr Gly Leu Gly Pro Ala  
20 25 30

656

Ala Arg Ser Cys Leu Pro Gln Pro Pro Ser Arg Gly Pro Gln Pro Pro  
           35                    40                    45  
 Pro Thr Leu Pro His Gly Pro Gly Ala Met Ser Glu Leu Glu Gln Leu  
           50                    55                    60  
 Arg Gln Glu Ala Glu Gln Leu Arg Asn Gln Ile Arg Asp Ala Arg Lys  
           65                    70                    75                    80  
 Ala Cys Gly Asp Ser Thr Leu Thr Gln Ile Thr Ala Gly Leu Asp Pro  
                     85                    90                    95  
 Val Gly Arg Ile Gln Met Arg Thr Arg Arg Thr Leu Arg Gly His Leu  
                     100                    105                    110  
 Ala Lys Ile Tyr Ala Met His Trp Gly Thr Asp Ser Arg Leu Leu Val  
           115                    120                    125  
 Ser Ala Ser Gln Asp Gly Lys Leu Ile Ile Trp Asp Ser Tyr Thr Thr  
           130                    135                    140  
 Asn Lys Val His Ala Ile Pro Leu Arg Ser Ser Trp Val Met Thr Cys  
           145                    150                    155                    160  
 Ala Tyr Ala Pro Ser Gly Asn Phe Val Ala Cys Gly Gly Leu Asp Asn  
                     165                    170                    175  
 Ile Cys Ser Ile Tyr Ser Leu Lys Thr Arg Glu Ala Thr Ser Gly Ser  
           180                    185                    190  
 Ala Gly Ser Cys Leu Ala Thr Leu Gly Thr Cys Arg Val Ala Ala Ser  
           195                    200                    205  
 Trp Met Thr Thr Lys Ser Ser Pro Ala Leu Gly Ile Pro Pro Val Pro  
           210                    215                    220  
 Cys Gly Thr Leu Arg Gln Ala Ser Arg Gln Trp Val Leu Leu Asp Thr  
           225                    230                    235                    240  
 Val Gly Met

&lt;210&gt; 683

&lt;211&gt; 146

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

657

&lt;222&gt; (133)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 683

Asp Leu Glu Gly Asp Ala Gly Tyr Thr Gly Gly Leu Arg Gln Gly His  
 1 5 10 15

Ala Gly Gly Ala Gly Glu Leu Ala Arg Thr Leu Ala Leu Lys Pro Thr  
 20 25 30

Ser Leu Glu Leu Phe Arg Thr Lys Val Asn Ala Leu Thr Tyr Gly Glu  
 35 40 45

Val Leu Arg Leu Arg Gln Thr Glu Arg Leu His Gln Glu Gly Thr Leu  
 50 55 60

Ala Pro Pro Ile Leu Glu Leu Arg Glu Lys Leu Lys Pro Glu Leu Met  
 65 70 75 80

Gly Leu Ile Arg Gln Gln Arg Leu Leu Arg Leu Cys Glu Gly Thr Leu  
 85 90 95

Phe Arg Lys Ile Ser Ser Arg Arg Gln Asp Lys Leu Trp Phe Cys  
 100 105 110

Cys Leu Ser Pro Asn His Lys Leu Leu Gln Tyr Gly Asp Met Glu Glu  
 115 120 125

Gly Ala Ser Ala Xaa Pro Trp Arg Val Cys Pro Ser Asn Ser Leu Trp  
 130 135 140

Pro Thr  
 145

&lt;210&gt; 684

&lt;211&gt; 300

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 684

Val Tyr Ser Cys Gly Phe Gln Val Gln Ser Trp Ser Pro Arg Trp Ile  
 1 5 10 15

Trp Val Thr Thr Lys Ser Lys Ile Gly Ala Pro Arg Ser Ser Phe Cys  
 20 25 30

Trp His Arg Leu Pro Ser Thr Ser Gln Leu His Leu Cys Pro Ala Glu  
 35 40 45

658

Gly Glu Ala Pro Ser Ala Gly Glu Ala Ala Pro Arg Ala Pro Thr Gly  
50 55 60

Ser Glu Pro Lys Pro Gly Ala Leu Pro Trp Gly Pro Arg Ala Pro Asp  
65 70 75 80

Ser Glu Gly Gly Gly Gly Ala Gly Ala Ala Asp Pro Ala Ala Asn Ala  
85 90 95

Gly His Gly Ala Ser Ser Glu Ala Glu Cys Gly Cys Gln Arg Thr Leu  
100 105 110

Arg Pro Met Pro Ser Thr Pro Gly Pro Gly Ala Ala Ala Val Arg Ala  
115 120 125

Leu Gly Gln Leu Phe His Ile Ala Cys Phe Thr Cys His Gln Cys Ala  
130 135 140

Gln Gln Leu Gln Gly Gln Gln Phe Tyr Ser Leu Glu Gly Ala Pro Tyr  
145 150 155 160

Cys Glu Gly Cys Tyr Thr Asp Thr Leu Glu Lys Cys Asn Thr Cys Gly  
165 170 175

Glu Pro Ile Thr Asp Arg Met Leu Arg Ala Thr Gly Lys Ala Tyr His  
180 185 190

Pro His Cys Phe Thr Cys Val Val Cys Ala Arg Pro Leu Glu Gly Thr  
195 200 205

Ser Phe Ile Val Asp Gln Ala Asn Arg Pro His Cys Val Pro Asp Tyr  
210 215 220

His Lys Gln Tyr Ala Pro Arg Cys Ser Val Cys Ser Glu Pro Ile Met  
225 230 235 240

Pro Glu Pro Gly Arg Asp Glu Thr Val Arg Val Val Ala Leu Asp Lys  
245 250 255

Asn Phe His Met Lys Cys Tyr Lys Cys Glu Asp Cys Gly Lys Pro Leu  
260 265 270

Ser Ile Glu Ala Asp Asp Asn Gly Cys Phe Pro Leu Asp Gly His Val  
275 280 285

Leu Cys Arg Lys Cys His Thr Ala Arg Ala Gln Thr  
290 295 300

&lt;210&gt; 685



659

<211> 130  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (61)  
<223> Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 685

Ile Arg His Glu Asp Cys Pro Thr Pro Ser Gln Cys Val Val Ala Arg  
1 5 10 15

Thr Leu Gly Lys Gln Gln Thr Val Met Ala Ile Ala Thr Lys Ile Ala  
20 25 30

Leu Gln Met Asn Cys Lys Met Gly Gly Glu Leu Trp Arg Val Asp Ile  
35 40 45

Pro Leu Lys Leu Val Met Ile Val Gly Ile Asp Cys Xaa His Asp Met  
50 55 60

Thr Ala Gly Arg Arg Ser Ile Ala Gly Phe Val Ala Ser Ile Asn Glu  
65 70 75 80

Gly Met Thr Arg Trp Phe Ser Arg Cys Ile Phe Gln Asp Arg Gly Gln  
85 90 95

Glu Leu Val Asp Gly Leu Lys Val Cys Leu Gln Ala Ala Leu Arg Ala  
100 105 110

Trp Asn Ser Cys Asn Glu Tyr Met Pro Ser Arg Ile Ile Val Tyr Arg  
115 120 125

Val Ala  
130

<210> 686  
<211> 207  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (84)  
<223> Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 686

Ile Tyr Gln Val Tyr Asn Ala Leu Gln Glu Lys Val Gln Ala Val Cys

660

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      1             5             10             15
Ala Asp Val Glu Lys Ser Glu Arg Val Val Glu Ser Cys Gln Ala Glu
      20             25             30
Val Asn Lys Leu Arg Arg Gln Ile Thr Gln Arg Lys Asn Glu Lys Glu
      35             40             45
Gln Glu Arg Arg Leu Gln Gln Ala Val Leu Ser Arg Gln Met Pro Ser
      50             55             60
Glu Ser Leu Asp Pro Ala Phe Ser Pro Arg Met Pro Ser Ser Gly Phe
      65             70             75             80
Ala Ala Glu Xaa Arg Ser Thr Leu Gly Asp Ala Glu Ala Ser Asp Pro
      85             90             95
Pro Pro Pro Tyr Ser Asp Phe His Pro Asn Asn Gln Glu Ser Thr Leu
      100            105            110
Ser His Ser Arg Met Glu Arg Ser Val Phe Met Pro Arg Pro Gln Ala
      115            120            125
Val Gly Ser Ser Asn Tyr Ala Ser Thr Ser Ala Gly Leu Lys Tyr Pro
      130            135            140
Gly Ser Gly Ala Asp Leu Pro Pro Pro Gln Arg Ala Ala Gly Asp Ser
      145            150            155            160
Gly Glu Asp Ser Asp Asp Ser Asp Tyr Glu Asn Leu Ile Asp Pro Thr
      165            170            175
Glu Pro Ser Asn Ser Glu Tyr Ser His Ser Lys Asp Ser Arg Pro Met
      180            185            190
Ala His Pro Asp Glu Asp Pro Arg Asn Thr Gln Thr Ser Gln Ile
      195            200            205

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&lt;210&gt; 687

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 687

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Ala Arg Ala Gly Glu Glu Gly Val Val Thr Arg Trp Arg His Arg Leu
      1             5             10             15
Gly Gln Gly Ala Cys Pro Trp Asp Arg Ser Arg Pro Met Glu Pro Pro
      20             25             30

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661

Gly Arg Ser Ser Arg Ser Thr Ala Ser His Thr Leu His Gln Tyr Cys  
           35                    40                    45  
 Cys Pro Thr Gln Val Leu Asp Ser Met Lys Leu Thr Pro Ser Gly Arg  
           50                    55                    60  
 Leu Ala Glu Ser Arg Glu Glu Glu Glu Glu Glu Thr Glu Glu Glu  
           65                    70                    75                    80  
 Glu Glu Glu Asp Ala His Gln Phe Cys Cys Pro Ala Ser Glu Cys Ser  
                     85                    90                    95  
 Ser Pro Ser Ser Arg  
                     100

<210> 688  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<400> 688  
 Glu Arg Asn Ala Asp Pro Pro Asp Val Ser Leu Gly Lys Ala Val Asn  
   1                    5                    10                    15  
 Gln Leu Ile Phe Ile Glu Asp Leu Leu Cys Pro Leu His Arg Val Ala  
           20                    25                    30  
 Ser Val Arg Glu Ser Trp Phe Phe Pro Arg Asn Thr Asp Phe Leu Ser  
           35                    40                    45  
 Gly Arg Leu His Val Phe Ile Tyr Phe His His Ser Arg Phe  
           50                    55                    60

<210> 689  
 <211> 549  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 689

Xaa	Arg	Trp	Ala	Cys	Gly	Xaa	Leu	Leu	Leu	Leu	Val	Arg	Gly	Gln	Gly
1				5				10						15	
Gln	Asp	Ser	Ala	Ser	Pro	Ile	Arg	Thr	Thr	His	Thr	Gly	Gln	Val	Leu
	20						25						30		
Gly	Ser	Leu	Val	His	Val	Lys	Gly	Ala	Asn	Ala	Gly	Val	Gln	Thr	Phe
	35					40					45				
Leu	Gly	Ile	Pro	Phe	Ala	Lys	Pro	Pro	Leu	Gly	Pro	Leu	Arg	Phe	Ala
	50					55				60					
Pro	Pro	Glu	Pro	Pro	Glu	Ser	Trp	Ser	Gly	Val	Arg	Asp	Gly	Thr	Thr
65					70				75					80	
His	Pro	Ala	Met	Cys	Leu	Gln	Asp	Leu	Thr	Ala	Val	Glu	Ser	Glu	Phe
			85					90						95	
Leu	Ser	Gln	Phe	Asn	Met	Thr	Phe	Pro	Ser	Asp	Ser	Met	Ser	Glu	Asp
	100							105					110		
Cys	Leu	Tyr	Leu	Ser	Ile	Tyr	Thr	Pro	Ala	His	Ser	His	Glu	Gly	Ser
	115						120					125			
Asn	Leu	Pro	Val	Met	Val	Trp	Ile	His	Gly	Gly	Ala	Leu	Val	Phe	Gly
	130					135					140				
Met	Ala	Ser	Leu	Tyr	Asp	Gly	Ser	Met	Leu	Ala	Ala	Leu	Glu	Asn	Val
145					150					155				160	
Val	Val	Val	Ile	Ile	Gln	Tyr	Arg	Leu	Gly	Val	Leu	Gly	Phe	Phe	Ser
			165					170					175		
Thr	Gly	Asp	Lys	His	Ala	Thr	Gly	Asn	Trp	Gly	Tyr	Leu	Asp	Gln	Val
		180						185					190		
Ala	Ala	Leu	Arg	Trp	Val	Gln	Gln	Asn	Ile	Ala	His	Phe	Gly	Gly	Asn
	195					200						205			
Pro	Asp	Arg	Val	Thr	Ile	Phe	Gly	Glu	Ser	Ala	Gly	Gly	Thr	Ser	Val
	210					215					220				
Ser	Ser	Leu	Val	Val	Ser	Pro	Ile	Ser	Gln	Gly	Leu	Phe	His	Gly	Ala
225					230					235				240	
Ile	Met	Glu	Ser	Gly	Val	Ala	Leu	Leu	Pro	Gly	Leu	Ile	Ala	Ser	Ser
			245						250					255	

Ala Asp Val Ile Ser Thr Val Val Ala Asn Leu Ser Ala Cys Asp Gln  
 260 265 270  
 Val Asp Ser Glu Ala Leu Val Gly Cys Leu Arg Gly Lys Ser Lys Glu  
 275 280 285  
 Glu Ile Leu Ala Ile Asn Lys Pro Phe Lys Met Ile Pro Gly Val Val  
 290 295 300  
 Asp Gly Val Phe Leu Pro Arg His Pro Gln Glu Leu Leu Ala Ser Ala  
 305 310 315 320  
 Asp Phe Gln Pro Val Pro Ser Ile Val Gly Val Asn Asn Asn Glu Phe  
 325 330 335  
 Gly Trp Leu Ile Pro Lys Val Met Arg Ile Tyr Asp Thr Gln Lys Glu  
 340 345 350  
 Met Asp Arg Glu Ala Ser Gln Ala Ala Leu Gln Lys Met Leu Thr Leu  
 355 360 365  
 Leu Met Leu Pro Pro Thr Phe Gly Asp Leu Leu Arg Glu Glu Tyr Ile  
 370 375 380  
 Gly Asp Asn Gly Asp Pro Gln Thr Leu Gln Ala Gln Phe Gln Glu Met  
 385 390 395 400  
 Met Ala Asp Ser Met Phe Val Ile Pro Ala Leu Gln Val Ala His Phe  
 405 410 415  
 Gln Cys Ser Arg Ala Pro Val Tyr Phe Tyr Glu Phe Gln His Gln Pro  
 420 425 430  
 Ser Trp Leu Lys Asn Ile Arg Pro Pro His Met Lys Ala Asp His Gly  
 435 440 445  
 Asp Glu Leu Pro Phe Val Phe Arg Ser Phe Phe Gly Gly Asn Tyr Ile  
 450 455 460  
 Lys Phe Thr Glu Glu Glu Glu Gln Leu Ser Arg Lys Met Met Lys Tyr  
 465 470 475 480  
 Trp Ala Asn Phe Ala Arg Asn Gly Asn Pro Asn Gly Glu Gly Leu Pro  
 485 490 495  
 His Trp Pro Leu Phe Asp Gln Glu Glu Gln Tyr Leu Gln Leu Asn Leu  
 500 505 510  
 Gln Pro Ala Val Gly Arg Ala Leu Lys Ala His Arg Leu Gln Phe Trp  
 515 520 525

664

Lys Lys Ala Leu Pro Gln Lys Ile Gln Glu Leu Glu Glu Pro Glu Glu  
 530 535 540

Arg His Thr Glu Leu  
 545

&lt;210&gt; 690

&lt;211&gt; 155

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (36)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (85)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 690

Ser His Arg Val Thr His Cys Pro Tyr Ala Val Ala Leu Pro Glu Val  
 1 5 10 15

Ala Pro Ala Gln Pro Leu Thr Glu Ala Leu Arg Ala Leu Cys His Val  
 20 25 30

Gly Leu Phe Xaa Phe Ala Phe Cys Ala Leu Phe Asp Cys Xaa Arg Pro  
 35 40 45

Val Xaa Gln Lys Ser Cys Asp Leu Leu Leu Phe Leu Arg Asp Lys Ile  
 50 55 60

Ala Ser Tyr Ser Ser Leu Arg Glu Ala Arg Gly Ser Pro Asn Thr Ala  
 65 70 75 80

Ser Ala Glu Ala Xaa Leu Pro Arg Trp Arg Ala Gly Glu Gln Ala Gln  
 85 90 95

665

Pro Pro Gly Asp Gln Glu Pro Glu Ala Val Leu Ala Met Leu Arg Ser  
100 105 110

Leu Asp Leu Glu Gly Leu Arg Ser Thr Leu Ala Glu Ser Ser Asp His  
115 120 125

Val Glu Lys Ser Pro Gln Ser Leu Leu Gln Asp Met Leu Ala Thr Gly  
130 135 140

Gly Phe Leu Gln Gly Asp Glu Ala Asp Cys Tyr  
145 150 155

&lt;210&gt; 691

&lt;211&gt; 149

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 691

Met Cys Leu Glu Arg Pro Leu Arg Glu Gly Pro Arg Val Met Glu Lys  
1 5 10 15

Glu Ala Trp Pro Gly Ser Leu Glu Gly Arg Gly Gly Gly Trp Arg His  
20 25 30

Leu Asp Cys Pro Leu Leu Ser His Thr Trp Gly Val Val Thr Pro Phe  
35 40 45

Thr Pro Ala Arg Leu Pro Ser Ala Phe His Glu Leu His Leu Leu Pro  
50 55 60

Thr Ser Leu Trp Arg Gly Trp Gly Pro Leu Ala Ser Thr Arg Gly Pro  
65 70 75 80

Ser Ala Ser Pro Lys Pro Glu Pro Ser Ala Pro Gly Glu Asn Lys Trp  
85 90 95

Leu Ser Phe Asp Thr Trp Gly Arg Arg Glu Ala Ala Gly Trp Arg Gln  
100 105 110

Ser Gln Gly Arg Asp Thr Thr Glu Gly Asp Pro Asp Ile Pro Arg Lys  
115 120 125

Phe Pro Ala Glu Gln Thr Ala Phe Gln Pro Glu Ala Cys Leu Asn Cys  
130 135 140

Val Met Cys Asn Asn  
145

666

<210> 692  
<211> 218  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (160)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 692  
Pro Gly Val Lys Leu Trp Asp Val Pro Val Met Leu Asp His Lys Asp  
1 5 10 15  
Leu Glu Ala Glu Ile His Pro Leu Lys Asn Glu Glu Arg Lys Ser Gln  
20 25 30  
Glu Asn Leu Gly Asn Pro Ser Lys Asn Glu Asp Asn Val Lys Ser Ala  
35 40 45  
Pro Pro Gln Ser Arg Leu Ser Arg Cys Arg Ala Ala Phe Phe Leu  
50 55 60  
Ser Leu Phe Leu Cys Leu Phe Val Val Phe Val Val Ser Phe Val Ile  
65 70 75 80  
Pro Cys Pro Asp Arg Pro Ala Ser Gln Arg Met Trp Arg Ile Asp Tyr  
85 90 95  
Ser Ala Ala Val Ile Tyr Asp Phe Leu Ala Val Asp Asp Ile Asn Gly  
100 105 110  
Asp Arg Ile Gln Asp Val Leu Phe Leu Tyr Lys Asn Thr Asn Ser Ser  
115 120 125  
Asn Asn Phe Ser Arg Ser Cys Val Asp Glu Gly Phe Ser Ser Pro Cys  
130 135 140  
Thr Phe Ala Ala Ala Val Ser Gly Ala Asn Ala Ala Arg Ser Gly Xaa  
145 150 155 160  
Asp Leu Trp Pro Lys Thr Trp Pro Ser Trp Ser Val Leu Cys Pro Ser  
165 170 175  
Gln Glu Ala Val Arg His Leu Leu Pro Ala Ser Trp Trp Ala Asp Pro  
180 185 190  
Val Leu Ser Leu Gln Ser Thr Cys Ser Gln Gly Lys Pro Trp Lys Pro  
195 200 205



667

Gln Pro Ala Val Gln Gly Glu Trp Ser Ile  
210 215

&lt;210&gt; 693

&lt;211&gt; 68

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 693

Ser Cys Asn Ser Ser Asn Asn Ile Leu Gln Leu Pro Tyr Arg Asn Arg  
1 5 10 15

Ser Gly Arg Ala Lys Ser Asp Leu Gly Lys Val Ile Arg Tyr Arg Leu  
20 25 30

Ser Ile Pro Phe Pro Lys Met Leu Gly Thr Arg Ser Ile Ser Asp Phe  
35 40 45

Ile Ile Phe Phe Lys Val Trp Asn Ile Cys Ile Ile Leu Thr Ser Trp  
50 55 60

Ala Ser Gln Ile  
65

&lt;210&gt; 694

&lt;211&gt; 234

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (4)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (219)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 694

Cys Ala Xaa Xaa Leu Arg Gly Phe Asp Gln Gln Met Ser Ser Met Val

668

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      1             5             10             15
Ile Glu His Met Ala Ser His Gly Thr Arg Phe Leu Arg Gly Cys Ala
      20             25             30
Pro Ser Arg Val Arg Arg Leu Pro Asp Gly Gln Leu Gln Val Thr Trp
      35             40             45
Glu Asp Ser Thr Thr Gly Lys Glu Asp Thr Gly Thr Phe Asp Thr Val
      50             55             60
Leu Trp Ala Ile Gly Arg Val Pro Asp Thr Arg Ser Leu Asn Leu Glu
      65             70             75             80
Lys Ala Gly Val Asp Thr Ser Pro Asp Thr Gln Lys Ile Leu Val Asp
      85             90             95
Ser Arg Glu Ala Thr Ser Val Pro His Ile Tyr Ala Ile Gly Asp Val
      100            105            110
Val Glu Gly Arg Pro Glu Leu Thr Pro Thr Ala Ile Met Ala Gly Arg
      115            120            125
Leu Leu Val Gln Arg Leu Phe Gly Gly Ser Ser Asp Leu Met Asp Tyr
      130            135            140
Asp Asn Val Pro Thr Thr Val Phe Thr Pro Leu Glu Tyr Gly Cys Val
      145            150            155            160
Gly Leu Ser Glu Glu Glu Ala Val Ala Arg His Gly Gln Glu His Val
      165            170            175
Glu Val Tyr His Ala His Tyr Lys Pro Leu Glu Phe Thr Val Ala Gly
      180            185            190
Arg Asp Ala Ser Gln Cys Tyr Val Lys Met Val Cys Leu Arg Glu Pro
      195            200            205
Pro Gln Leu Val Leu Gly Leu His Phe Leu Xaa Pro Thr Gln Ala Asn
      210            215            220
Tyr Ser Arg Ile Cys Ser Gly Asp Lys Cys
      225            230

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&lt;210&gt; 695

&lt;211&gt; 460

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

669

&lt;400&gt; 695

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Pro Cys Pro Pro Arg Pro Gln Glu Leu Pro Gly Arg Ser Pro Ser Ser
 1           5           10           15

Trp Ser Ala Leu Gly Trp Pro Ala Ala Leu Gly Gly Gly Val Val Ala
      20           25           30

Val Ala Val Cys Glu Pro Val Ala Arg Leu Leu Trp Ala Gly Thr Leu
      35           40           45

Lys Ile Ala Ala Met Ala Glu Asn Gly Asp Asn Glu Lys Met Ala Ala
      50           55           60

Leu Glu Ala Lys Ile Cys His Gln Ile Glu Tyr Tyr Phe Gly Asp Phe
      65           70           75           80

Asn Leu Pro Arg Asp Lys Phe Leu Lys Glu Gln Ile Lys Leu Asp Glu
      85           90           95

Gly Trp Val Pro Leu Glu Ile Met Ile Lys Phe Asn Arg Leu Asn Arg
      100           105           110

Leu Thr Thr Asp Phe Asn Val Ile Val Glu Ala Leu Ser Lys Ser Lys
      115           120           125

Ala Glu Leu Met Glu Ile Ser Glu Asp Lys Thr Lys Ile Arg Arg Ser
      130           135           140

Pro Ser Lys Pro Leu Pro Glu Val Thr Asp Glu Tyr Lys Asn Asp Val
      145           150           155           160

Lys Asn Arg Ser Val Tyr Ile Lys Gly Phe Pro Thr Asp Ala Thr Leu
      165           170           175

Asp Asp Ile Lys Glu Trp Leu Glu Asp Lys Gly Gln Val Leu Asn Ile
      180           185           190

Gln Met Arg Arg Thr Leu His Lys Ala Phe Lys Gly Ser Ile Phe Val
      195           200           205

Val Phe Asp Ser Ile Glu Ser Ala Lys Lys Phe Val Glu Thr Pro Gly
      210           215           220

Gln Lys Tyr Lys Glu Thr Asp Leu Leu Ile Leu Phe Lys Asp Asp Tyr
      225           230           235           240

Phe Ala Lys Lys Asn Glu Glu Arg Lys Gln Asn Lys Val Glu Ala Lys
      245           250           255

Leu Arg Ala Lys Gln Glu Gln Glu Ala Lys Gln Lys Leu Glu Glu Asp
      260           265           270

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670

Ala Glu Met Lys Ser Leu Glu Glu Lys Ile Gly Cys Leu Leu Lys Phe  
 275 280 285  
 Ser Gly Asp Leu Asp Asp Gln Thr Cys Arg Glu Asp Leu His Ile Leu  
 290 295 300  
 Phe Ser Asn His Gly Glu Ile Lys Trp Ile Asp Phe Val Arg Gly Ala  
 305 310 315 320  
 Lys Glu Gly Ile Ile Leu Phe Lys Glu Lys Ala Lys Glu Ala Leu Gly  
 325 330 335  
 Lys Ala Lys Asp Ala Asn Asn Gly Asn Leu Gln Leu Arg Asn Lys Glu  
 340 345 350  
 Val Thr Trp Glu Val Leu Glu Gly Glu Val Glu Lys Glu Ala Leu Lys  
 355 360 365  
 Lys Ile Ile Glu Asp Gln Gln Glu Ser Leu Asn Lys Trp Lys Ser Lys  
 370 375 380  
 Gly Arg Arg Phe Lys Gly Lys Gly Lys Gly Asn Lys Ala Ala Gln Pro  
 385 390 395 400  
 Gly Ser Gly Lys Gly Lys Val Gln Phe Gln Gly Lys Lys Thr Lys Phe  
 405 410 415  
 Ala Ser Asp Asp Glu His Asp Glu His Asp Glu Asn Gly Ala Thr Gly  
 420 425 430  
 Pro Val Lys Arg Ala Arg Glu Glu Thr Asp Lys Glu Glu Pro Ala Ser  
 435 440 445  
 Lys Gln Gln Lys Thr Glu Asn Gly Ala Gly Asp Gln  
 450 455 460

&lt;210&gt; 696

&lt;211&gt; 80

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 696

Gly Glu Glu Gly Val Gly Ser Pro Ser Gly Ile Leu Ala Thr Pro Leu  
 1 5 10 15  
 Arg Ser Ala Arg Gly Thr Thr His Thr His Thr His Thr His Thr His  
 20 25 30

671

Thr His Ser His Thr His Ala His Phe Pro Ser Phe Pro Asp Pro Leu  
           35                  40                  45

Phe Gln Ser Ser Pro Phe Ser Ser Gly Phe Ile Asp Glu Tyr Lys Tyr  
       50                  55                  60

Pro His Leu Trp Pro Val Met Ser Val Thr Cys Cys Arg Phe Cys Val  
       65                  70                  75                  80

&lt;210&gt; 697

&lt;211&gt; 257

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 697

Trp Pro Arg Arg Pro Gly Pro His Leu Gly Val Leu Glu Phe Pro Gly  
   1                  5                  10                  15

Ala Gly Cys Gly Ala Ser Ala Ala Gly Trp Pro Ser Ala Xaa Met Leu  
           20                  25                  30

Pro Gly Arg Gly Pro Arg Pro Phe Arg Ala Arg Leu Val Gly Arg Glu  
       35                  40                  45

Leu Val Ser Met Leu Ala Arg Glu Leu Pro Ala Ala Val Ala Pro Ala  
       50                  55                  60

Gly Pro Ala Ser Leu Ala Arg Trp Thr Leu Gly Phe Cys Asp Glu Arg  
       65                  70                  75                  80

Leu Val Pro Phe Asp His Ala Glu Ser Thr Tyr Gly Leu Tyr Arg Thr  
           85                  90                  95

His Leu Leu Ser Arg Leu Pro Ile Pro Glu Ser Gln Val Ile Thr Ile  
       100                  105                  110

Asn Pro Glu Leu Pro Val Glu Glu Ala Ala Glu Asp Tyr Ala Lys Lys  
       115                  120                  125

Leu Arg Gln Ala Phe Gln Gly Asp Ser Ile Pro Val Phe Asp Leu Leu  
       130                  135                  140

672

Ile Leu Gly Val Gly Pro Asp Gly His Thr Cys Ser Leu Phe Pro Asp  
 145 150 155 160  
 His Pro Leu Leu Gln Glu Arg Glu Lys Ile Val Ala Pro Ile Ser Asp  
 165 170 175  
 Ser Pro Lys Pro Pro Pro Gln Arg Val Thr Leu Thr Leu Pro Val Leu  
 180 185 190  
 Asn Ala Ala Arg Thr Val Ile Phe Val Ala Thr Gly Glu Gly Lys Ala  
 195 200 205  
 Ala Val Leu Lys Arg Ile Leu Glu Asp Gln Glu Glu Asn Pro Leu Pro  
 210 215 220  
 Ala Ala Leu Val Gln Pro His Thr Gly Lys Leu Cys Trp Phe Leu Asp  
 225 230 235 240  
 Glu Ala Ala Ala Arg Leu Leu Thr Val Pro Phe Glu Lys His Ser Thr  
 245 250 255  
 Leu

<210> 698  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<400> 698  
 Gln Tyr Lys Thr Pro Ala Val Asp Thr Thr Met Met Thr Phe His Glu  
 1 5 10 15  
 Leu Val Phe Leu Val Leu Thr Ala Lys Phe Val Leu Phe Thr Gly Gln  
 20 25 30  
 Ile Ser Asn Lys Val Leu Gly Leu Lys Ile His Gly Trp Thr Glu Val  
 35 40 45  
 Pro Tyr Pro Leu Thr Met Glu Ala Gly Ala Thr Phe Trp Gly Tyr Leu  
 50 55 60  
 Phe Leu Asn Phe  
 65

<210> 699

673

&lt;211&gt; 360

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 699

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Pro Cys Ser Ala Thr Thr Ala Trp Val Lys Ser Ser Ile Lys Thr His
  1             5             10             15

Leu Cys Ala Ser Leu Arg His Ile Arg Phe Leu Leu Ser Val Cys Leu
      20             25             30

Leu Cys Leu Val Ala Gly Thr Ala Val Ala Val Lys Met Ala Ser Thr
      35             40             45

Ser Arg Leu Asp Ala Leu Pro Arg Val Thr Cys Pro Asn His Pro Asp
      50             55             60

Ala Ile Leu Val Glu Asp Tyr Arg Ala Gly Asp Met Ile Cys Pro Glu
      65             70             75             80

Cys Gly Leu Val Val Gly Asp Arg Val Ile Asp Val Gly Ser Glu Trp
      85             90             95

Arg Thr Phe Ser Asn Asp Lys Ala Thr Lys Asp Pro Ser Arg Val Gly
      100            105            110

Asp Ser Gln Asn Pro Leu Leu Ser Asp Gly Asp Leu Ser Thr Met Ile
      115            120            125

Gly Lys Gly Thr Gly Ala Ala Ser Phe Asp Glu Phe Gly Asn Ser Lys
      130            135            140

Tyr Gln Asn Arg Arg Thr Met Ser Ser Ser Asp Arg Ala Met Met Asn
      145            150            155            160

Ala Phe Lys Glu Ile Thr Thr Met Ala Asp Arg Ile Asn Leu Pro Arg
      165            170            175

Asn Ile Val Asp Arg Thr Asn Asn Leu Phe Lys Gln Val Tyr Glu Gln
      180            185            190

Lys Ser Leu Lys Gly Arg Ala Asn Asp Ala Ile Ala Ser Ala Cys Leu
      195            200            205

Tyr Ile Ala Cys Arg Gln Glu Gly Val Pro Arg Thr Phe Lys Glu Ile
      210            215            220

Cys Ala Val Ser Arg Ile Ser Lys Lys Glu Ile Gly Arg Cys Phe Lys
      225            230            235            240

Leu Ile Leu Lys Ala Leu Glu Thr Ser Val Asp Leu Ile Thr Thr Gly

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674

245 250 255  
Asp Phe Met Ser Arg Phe Cys Ser Asn Leu Cys Leu Pro Lys Gln Val  
260 265 270  
Gln Met Ala Ala Thr His Ile Ala Arg Lys Ala Val Glu Leu Asp Leu  
275 280 285  
Val Pro Gly Arg Ser Pro Ile Ser Val Ala Ala Ala Ala Ile Tyr Met  
290 295 300  
Ala Ser Gln Ala Ser Ala Glu Lys Arg Thr Gln Lys Glu Ile Gly Asp  
305 310 315 320  
Ile Ala Gly Val Ala Asp Val Thr Ile Arg Gln Ser Tyr Arg Leu Ile  
325 330 335  
Tyr Pro Arg Ala Pro Asp Leu Phe Pro Thr Asp Phe Lys Phe Asp Thr  
340 345 350  
Pro Val Asp Lys Leu Pro Gln Leu  
355 360

&lt;210&gt; 700

&lt;211&gt; 364

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (13)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (30)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (353)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (360)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 700



675

Pro Ser Trp Leu Arg Ala Arg Ser Ser Arg Ser Trp Xaa Ala Ser Pro  
 1 5 10 15  
 Arg Gly Pro Gln Pro Pro Arg Ile Arg Ala Arg Ser Ala Xaa Pro Met  
 20 25 30  
 Glu Gly Ala Arg Val Phe Gly Ala Leu Gly Pro Ile Gly Pro Ser Ser  
 35 40 45  
 Pro Gly Leu Thr Leu Gly Gly Leu Ala Val Ser Glu His Arg Leu Ser  
 50 55 60  
 Asn Lys Leu Leu Ala Trp Ser Gly Val Leu Glu Trp Gln Glu Lys Arg  
 65 70 75 80  
 Arg Pro Tyr Ser Asp Ser Thr Ala Lys Leu Lys Arg Thr Leu Pro Cys  
 85 90 95  
 Gln Ala Tyr Val Asn Gln Gly Glu Asn Leu Glu Thr Asp Gln Trp Pro  
 100 105 110  
 Gln Lys Leu Ile Met Gln Leu Ile Pro Gln Gln Leu Leu Thr Thr Leu  
 115 120 125  
 Gly Pro Leu Phe Arg Asn Ser Gln Leu Ala Gln Phe His Phe Thr Asn  
 130 135 140  
 Arg Asp Cys Asp Ser Leu Lys Gly Leu Cys Arg Ile Met Gly Asn Gly  
 145 150 155 160  
 Phe Ala Gly Cys Met Leu Phe Pro His Ile Ser Pro Cys Glu Val Arg  
 165 170 175  
 Val Leu Met Leu Leu Tyr Ser Ser Lys Lys Lys Ile Phe Met Gly Leu  
 180 185 190  
 Ile Pro Tyr Asp Gln Ser Gly Phe Val Ser Ala Ile Arg Gln Val Ile  
 195 200 205  
 Thr Thr Arg Lys Gln Ala Val Gly Pro Gly Gly Val Asn Ser Gly Pro  
 210 215 220  
 Val Gln Ile Val Asn Asn Lys Phe Leu Ala Trp Ser Gly Val Met Glu  
 225 230 235 240  
 Trp Gln Glu Pro Arg Pro Glu Pro Asn Ser Arg Ser Lys Arg Trp Leu  
 245 250 255  
 Pro Ser His Val Tyr Val Asn Gln Gly Glu Ile Leu Arg Thr Glu Gln  
 260 265 270

676

Trp Pro Arg Lys Leu Tyr Met Gln Leu Ile Pro Gln Gln Leu Leu Thr  
275 280 285  
Thr Leu Val Pro Leu Phe Arg Asn Ser Arg Leu Val Gln Phe His Phe  
290 295 300  
Thr Lys Asp Leu Glu Thr Leu Lys Ser Leu Cys Arg Ile Met Asp Asn  
305 310 315 320  
Gly Phe Ala Gly Cys Val His Phe Ser Tyr Lys Ala Ser Cys Glu Ile  
325 330 335  
Arg Val Leu Met Leu Leu Tyr Ser Ser Glu Lys Lys Ile Phe Ile Gly  
340 345 350  
Xaa Ile Pro His Asp Gln Gly Xaa Phe Val Gln Arg  
355 360

&lt;210&gt; 701

&lt;211&gt; 156

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (33)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 701

Gly Thr Arg Gly Ile Leu His Val Ala Val Pro Ala Arg Gly Thr His  
1 5 10 15  
Ala Gln Cys Cys Arg Asn Trp Thr Val Pro Asp Ser Gly Gln Gly Lys  
20 25 30  
Xaa Val Met Leu Glu Gly Gln Gly Arg Leu Glu Arg Val His Ile Pro  
35 40 45  
Leu Ser Ala Pro Ala Ser Ala Thr Val Gln Arg Pro Thr Gly Pro Gln  
50 55 60  
Pro Val Ala Cys Pro His Cys Pro Val Pro Thr Ser Asn Ser Pro Gln  
65 70 75 80  
Pro Leu Val Ala Ser Val Pro Cys Pro Leu Gly Phe Ser Ser Gln Pro  
85 90 95  
Ser Gly Leu Gly Leu Cys Arg Lys Val Met Pro Thr Gly Thr Leu Leu  
100 105 110

677

Thr Pro Gly Ser Phe Met Asp Val Val Ser Glu Leu Arg Thr Arg Gly  
 115 120 125

Cys Gln Met Phe Leu Ala Pro His Val Ser Phe Arg Thr Glu Gln Lys  
 130 135 140

His Lys Asp Ser Ala Lys Ser Ser Leu Tyr Ser Leu  
 145 150 155

&lt;210&gt; 702

&lt;211&gt; 150

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 702

Ala Gly His Gly Leu Gly Val Arg Ala Gly Leu Lys Glu Phe Ala Thr  
 1 5 10 15

Asn Leu Thr Glu Ser Gly Val His Gly Ala Leu Leu Ala Leu Asp Glu  
 20 25 30

Thr Phe Asp Tyr Ser Asp Leu Ala Leu Leu Leu Gln Ile Pro Thr Gln  
 35 40 45

Asn Ala Gln Ala Arg Gln Leu Leu Glu Lys Glu Phe Ser Asn Leu Ile  
 50 55 60

Ser Leu Gly Thr Asp Arg Arg Leu Asp Glu Asp Ser Ala Lys Ser Phe  
 65 70 75 80

Ser Arg Ser Pro Ser Trp Arg Lys Met Phe Arg Glu Lys Asp Leu Arg  
 85 90 95

Gly Val Thr Pro Asp Ser Ala Glu Met Leu Pro Pro Asn Phe Arg Ser  
 100 105 110

Ala Ala Ala Gly Ala Leu Gly Ser Pro Gly Leu Pro Leu Arg Lys Leu  
 115 120 125

Gln Pro Glu Gly Gln Thr Ser Gly Ser Ser Arg Ala Asp Gly Val Ser  
 130 135 140

Val Arg Thr Tyr Ser Cys  
 145 150

&lt;210&gt; 703

<211> 527  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (243)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (257)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (259)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (471)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (477)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (480)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (484)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (511)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (519)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 703  
Cys Val Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr

679

1	5	10	15
Arg Gly Tyr Ser Gly Val Phe Pro Asp Cys Thr Pro Cys His Gln Cys	20	25	30
Phe Ala Leu Trp Asp Val Ile Ile Ala Glu Leu Thr Asn Arg Thr His	35	40	45
Arg Phe Leu Glu Lys Ala Lys Ala Leu Lys Ile Ser Gly Val Ile Gly	50	55	60
Pro Tyr Arg Glu Thr Val Asp Ser Val Glu Arg Lys Val Ser Glu Ile	65	70	75
Lys Asp Ile Leu Ala Gln Ser Pro Ala Ala Glu Pro Leu Lys Asn Ile	85	90	95
Gly Asn Leu Phe Glu Glu Ala Glu Lys Leu Ile Lys Asp Val Thr Glu	100	105	110
Met Met Ala Gln Val Glu Val Lys Leu Ser Asp Thr Thr Ser Gln Ser	115	120	125
Asn Ser Thr Ala Lys Glu Leu Asp Ser Leu Gln Thr Glu Ala Glu Ser	130	135	140
Leu Asp Asn Thr Val Lys Glu Leu Ala Glu Gln Leu Glu Phe Ile Lys	145	150	155
Asn Ser Asp Ile Arg Gly Ala Leu Asp Ser Ile Thr Lys Tyr Phe Gln	165	170	175
Met Ser Leu Glu Ala Glu Glu Arg Val Asn Ala Ser Thr Thr Glu Pro	180	185	190
Asn Ser Thr Val Glu Gln Ser Ala Leu Met Arg Asp Arg Val Glu Asp	195	200	205
Val Met Met Glu Arg Glu Ser Gln Phe Lys Glu Lys Gln Glu Glu Gln	210	215	220
Ala Arg Leu Leu Asp Glu Leu Ala Gly Lys Leu Gln Ser Leu Asp Leu	225	230	235
Ser Ala Xaa Ala Glu Met Thr Cys Gly Thr Pro Pro Gly Ala Ser Cys	245	250	255
Xaa Glu Xaa Glu Cys Gly Gly Pro Asn Cys Arg Thr Asp Glu Gly Glu	260	265	270
Arg Lys Cys Gly Gly Pro Gly Cys Gly Gly Leu Val Thr Val Ala His			

680

275                      280                      285  
Asn Ala Trp Gln Lys Ala Met Asp Leu Asp Gln Asp Val Leu Ser Ala  
290                      295                      300  
Leu Ala Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys Leu  
305                      310                      315                      320  
Arg Ala Asp Glu Ala Lys Gln Ser Ala Glu Asp Ile Leu Leu Lys Thr  
325                      330                      335  
Asn Ala Thr Lys Glu Lys Met Asp Lys Ser Asn Glu Glu Leu Arg Asn  
340                      345                      350  
Leu Ile Lys Gln Ile Arg Asn Phe Leu Thr Gln Asp Ser Ala Asp Leu  
355                      360                      365  
Asp Ser Ile Glu Ala Val Ala Asn Glu Val Leu Lys Met Glu Met Pro  
370                      375                      380  
Ser Thr Pro Gln Gln Leu Gln Asn Leu Thr Glu Asp Ile Arg Glu Arg  
385                      390                      395                      400  
Val Glu Ser Leu Ser Gln Val Glu Val Ile Leu Gln His Ser Ala Ala  
405                      410                      415  
Asp Ile Ala Arg Ala Glu Met Leu Leu Glu Glu Ala Lys Arg Ala Ser  
420                      425                      430  
Lys Ser Ala Thr Asp Val Lys Val Thr Ala Asp Met Val Lys Glu Ala  
435                      440                      445  
Leu Glu Glu Ala Glu Lys Ala Gln Val Ala Ala Glu Lys Ala Ile Lys  
450                      455                      460  
Gln Ala Asp Glu Asp Ile Xaa Arg Asn Pro Glu Pro Xaa Asn Phe Xaa  
465                      470                      475                      480  
Leu Glu Phe Xaa Lys Gln Gln Leu Ser Gly Gly Asn Leu Val Gln Arg  
485                      490                      495  
Val Pro Arg Ala Ser Ser Glu Phe Arg Glu Asp Val Gly Arg Xaa Leu  
500                      505                      510  
Ser Gly Lys Leu Ala Gln Xaa Pro Gly Gly Gly Arg Ile Phe Trp  
515                      520                      525

&lt;210&gt; 704

&lt;211&gt; 62

681

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 704

Val Tyr Gln Arg Lys Ser Thr Val Val Leu Gly Gly Phe Leu Leu Trp  
 1 5 10 15

Asp Ile Asp Phe Leu Phe Phe Phe Arg Asn Ile Val Cys Cys Asn Leu  
 20 25 30

Asn Lys Asn Tyr Asp Ile Leu Arg Tyr Phe Ile Asp Lys Pro Asn Lys  
 35 40 45

Asn Ile Cys Phe Tyr Phe Lys Val Asn Val Phe Leu Phe Ser  
 50 55 60

&lt;210&gt; 705

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 705

Thr Glu Asp Leu Phe Gly Phe Lys His Leu Leu Arg Gln Tyr Leu Leu  
 1 5 10 15

Gly Lys Pro Asn Ile Ala Asn Gly Gln Phe Asp Phe Asn Phe Ser Lys  
 20 25 30

Asp Thr Leu Leu Ser Arg Arg Leu Lys Cys Leu His  
 35 40

&lt;210&gt; 706

&lt;211&gt; 193

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 706

Xaa Gly Arg Ala Trp Val Met Ala Ala Pro Gly Ala Leu Leu Val Met  
 1 5 10 15

Gly Val Ser Gly Ser Gly Lys Ser Thr Val Gly Ala Leu Leu Ala Ser  
 20 25 30

682

Glu Leu Gly Trp Lys Phe Tyr Asp Ala Asp Asp Tyr His Pro Glu Glu  
           35                          40                          45  
 Asn Arg Arg Lys Met Gly Lys Gly Ile Pro Leu Asn Asp Gln Asp Arg  
           50                          55                          60  
 Ile Pro Trp Leu Cys Asn Leu His Asp Ile Leu Leu Arg Asp Val Ala  
           65                          70                          75                          80  
 Ser Gly Gln Arg Val Val Leu Ala Cys Ser Ala Leu Lys Lys Thr Tyr  
                           85                          90                          95  
 Arg Asp Ile Leu Thr Gln Gly Lys Asp Gly Val Ala Leu Lys Cys Glu  
                           100                          105                          110  
 Glu Ser Gly Lys Glu Ala Lys Gln Ala Glu Met Gln Leu Leu Val Val  
           115                          120                          125  
 His Leu Ser Gly Ser Phe Glu Val Ile Ser Gly Arg Leu Leu Lys Arg  
           130                          135                          140  
 Glu Gly His Phe Met Pro Pro Glu Leu Leu Gln Ser Gln Phe Glu Thr  
           145                          150                          155                          160  
 Leu Glu Pro Pro Ala Ala Pro Glu Asn Phe Ile Gln Ile Ser Val Asp  
                           165                          170                          175  
 Lys Asn Val Ser Glu Ile Ile Ala Thr Ile Met Glu Thr Leu Lys Met  
           180                          185                          190

Lys

&lt;210&gt; 707

&lt;211&gt; 121

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (102)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (103)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids



683

&lt;400&gt; 707

Gly Ile Arg Gly Gln Thr Leu Trp Leu Gly Pro Leu Gly Ala Thr Leu  
 1 5 10 15  
 Trp Pro Leu Gly Ala Leu Glu Thr Ser His Val Leu Trp Ala Leu Trp  
 20 25 30  
 Arg Ala Leu Ala Leu His Gly Gly Ala Gly Arg His Cys Leu Pro Cys  
 35 40 45  
 Pro Leu Pro Ala Ala Pro Ala Leu Val Cys Arg Leu Gly Pro Gly Cys  
 50 55 60  
 Leu Leu Leu Gly Val Trp Pro Arg Ala Pro Val Lys Pro Trp Arg His  
 65 70 75 80  
 Cys Val Cys Val Met Gly Ser Glu Gly Leu Val Gly Ala Val His Trp  
 85 90 95  
 Ser Ser Ser Leu Pro Xaa Xaa Ala Ile Ser Met Ala Pro Phe Ala Ala  
 100 105 110  
 Glu Asp Thr His Cys Gly Ser Val Gly  
 115 120

&lt;210&gt; 708

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 708

Asn Ser Phe Cys Tyr Phe His Ile Arg Val Gln Thr Tyr Lys Gly Ala  
 1 5 10 15  
 Cys Ser Leu Lys Val His Asn Tyr Ser Tyr Ser Val Cys Leu Tyr Cys  
 20 25 30  
 Tyr Arg Met Leu Cys Phe Gly Ala Leu Ser Ser Ala Asp Pro Arg Ser  
 35 40 45  
 Ser Val Glu Ile His Cys Leu Gly His Ser Leu Ile Arg Met Leu Ala  
 50 55 60  
 Gly Asp Phe Val Ser Asp Val Ala Ser Leu Phe Ser Val His Arg Leu  
 65 70 75 80  
 Arg Val Thr Thr Val Ala Cys Arg Val His Pro Val Gly Ala Ala Gln  
 85 90 95

684

Leu Ser Glu Ser Lys Asn Leu Pro Thr Tyr Ser Asn Val Phe Ala Leu  
100 105 110

<210> 709  
<211> 72  
<212> PRT  
<213> Homo sapiens

<400> 709  
Arg Arg Val Trp Val Leu Phe Pro Pro Gln Arg Pro Glu Ser Gly Trp  
1 5 10 15  
Gly Val Ser Pro Val Glu Gly Glu Thr Val Pro Ala Leu Arg Gly Met  
20 25 30  
Lys Lys Ser Val Gly Leu Pro Val Ala Val Gln Cys Val Ala Leu Pro  
35 40 45  
Trp Gln Glu Glu Leu Cys Leu Arg Phe Met Arg Glu Val Glu Arg Leu  
50 55 60  
Met Thr Pro Glu Lys Gln Ser Ser  
65 70

<210> 710  
<211> 84  
<212> PRT  
<213> Homo sapiens

<400> 710  
Arg Leu His Arg Tyr Pro Glu Ala Met Ala Ser Lys Gly Leu Gln Asp  
1 5 10 15  
Leu Lys Gln Gln Val Glu Gly Thr Ala Gln Glu Ala Val Ser Ala Ala  
20 25 30  
Gly Ala Ala Ala Gln Gln Val Val Asp Gln Ala Thr Glu Ala Gly Gln  
35 40 45  
Lys Ala Met Asp Gln Leu Ala Lys Thr Thr Gln Glu Thr Ile Asp Lys  
50 55 60  
Thr Ala Asn Gln Ala Ser Asp Thr Phe Ser Gly Ile Gly Lys Lys Phe  
65 70 75 80

685

Gly Leu Leu Lys

&lt;210&gt; 711

&lt;211&gt; 63

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 711

Arg Leu His Arg Tyr Pro Glu Ala Met Ala Ser Lys Gly Leu Gln Asp  
1 5 10 15

Leu Lys Gln Gln Val Glu Gly Thr Ala Gln Glu Ala Ala Met Asp Gln  
20 25 30

Leu Ala Lys Thr Thr Gln Glu Thr Ile Asp Lys Thr Ala Asn Gln Ala  
35 40 45

Ser Asp Thr Phe Ser Gly Ile Gly Lys Lys Phe Gly Leu Leu Lys  
50 55 60

&lt;210&gt; 712

&lt;211&gt; 86

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 712

Arg Leu Ala Asn Arg Ala Ile Met Ser His Lys Gln Ile Tyr Tyr Ser  
1 5 10 15

Asp Lys Tyr Asp Asp Glu Glu Phe Glu Tyr Arg His Val Met Leu Pro  
20 25 30

Lys Asp Ile Ala Lys Leu Val Pro Lys Thr His Leu Met Ser Glu Ser  
35 40 45

Glu Trp Arg Asn Leu Gly Val Gln Gln Ser Gln Gly Trp Val His Tyr  
50 55 60

Met Ile His Glu Pro Glu Pro His Ile Leu Leu Phe Arg Arg Pro Leu  
65 70 75 80

Pro Lys Lys Pro Lys Lys  
85

686

<210> 713  
<211> 193  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (129)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 713  
Val Gln Lys Ala Gly Ala Arg Ala Leu Ala Val Ala Gly Ala Ala Arg  
1 5 10 15  
Thr Pro Arg Ser Leu Pro Gly Arg Pro Ala Val Cys Asn Met Thr Leu  
20 25 30  
Glu Glu Phe Ser Ala Gly Glu Gln Lys Thr Glu Arg Met Asp Lys Val  
35 40 45  
Gly Asp Ala Leu Glu Glu Val Leu Ser Lys Ala Leu Ser Gln Arg Thr  
50 55 60  
Ile Thr Val Gly Val Tyr Glu Ala Ala Lys Leu Leu Asn Val Asp Pro  
65 70 75 80  
Asp Asn Val Val Leu Cys Leu Leu Ala Ala Asp Glu Asp Asp Asp Arg  
85 90 95  
Asp Val Ala Leu Gln Ile His Phe Thr Leu Ile Gln Ala Phe Cys Cys  
100 105 110  
Glu Asn Asp Ile Asn Ile Leu Arg Val Thr Thr Arg Ala Gly Trp Arg  
115 120 125  
Xaa Pro Ala Leu Gly Asp Arg Arg Trp Pro Arg Gly Glu Arg Gly Arg  
130 135 140  
Arg Ala Ala Pro Gly Pro Ala Leu Arg Val Val Thr Asn Pro His Ser  
145 150 155 160  
Ser Gln Trp Lys Asp Pro Ala Leu Ser Gln Leu Ile Cys Phe Cys Arg  
165 170 175  
Glu Ser Arg Tyr Met Asp Gln Trp Val Pro Val Ile Asn Leu Pro Glu  
180 185 190  
Arg

<210> 714  
<211> 200  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (90)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (93)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (190)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 714  
Gly Pro Gly Ala Cys Ser Gly Pro Ala Pro Ser Pro Arg Arg Pro Gln  
1 5 10 15  
Ser Val Lys Cys Glu Pro Arg Arg Arg Gly Arg Ile Trp Pro Gly Ala  
20 25 30  
Gly Gly Gly Val Gly Ala Ala Arg His Val His His His Gln Gly Ala  
35 40 45  
Gln Gln Ala Gly Arg Ala Ala Pro His Arg Ser His Ala Ala Ala Gly  
50 55 60  
Gly Gly Pro Ala Arg Arg Ala Pro Glu Met Pro Ala Ala Arg Ala Ala  
65 70 75 80  
Asp Leu Ala Ala Pro Ala Gly Ala Ala Xaa Cys Ala Xaa Pro Gly Pro  
85 90 95  
Trp Pro Leu Ser Ser Pro Gly Pro Arg Leu Val Phe Asn Arg Val Asn  
100 105 110  
Gly Arg Arg Ala Pro Ser Thr Ser Pro Ser Phe Glu Gly Thr Gln Glu  
115 120 125  
Thr Tyr Thr Val Ala His Glu Glu Asn Val Arg Phe Val Ser Glu Ala  
130 135 140  
Trp Gln Gln Val Gln Gln Gln Leu Asp Gly Gly Pro Ala Gly Glu Gly

688

145                      150                      155                      160  
 Gly Pro Arg Pro Val Gln Tyr Val Glu Arg Thr Pro Asn Pro Arg Leu  
                                  165                      170                      175  
 Gln Asn Phe Val Pro Ile Asp Leu Asp Glu Trp Trp Ala Xaa Gln Phe  
                                  180                      185                      190  
 Leu Ala Arg Ile Thr Ser Cys Ser  
                                  195                      200

<210> 715  
 <211> 106  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (15)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 715  
 Trp Ile Pro Arg Ala Ala Gly Ile Arg His Glu Leu Val Pro Xaa Leu  
   1                                  5                                  10                                  15  
 Trp Ser Arg Glu Glu Ala Met Ala Thr Met Glu Asn Lys Val Ile Cys  
                                   20                                  25                                  30  
 Ala Leu Val Leu Val Ser Met Leu Ala Leu Gly Thr Leu Ala Glu Ala  
                                   35                                  40                                  45  
 Gln Thr Glu Thr Cys Thr Val Ala Pro Arg Glu Arg Gln Asn Cys Gly  
   50                                  55                                  60  
 Phe Pro Gly Val Thr Pro Ser Gln Cys Ala Asn Lys Gly Cys Cys Phe  
   65                                  70                                  75                                  80  
 Asp Asp Thr Val Arg Gly Val Pro Trp Cys Phe Tyr Pro Asn Thr Ile  
                                   85                                  90                                  95  
 Asp Val Pro Pro Glu Glu Glu Cys Glu Phe  
                                   100                                  105

<210> 716  
 <211> 105  
 <212> PRT  
 <213> Homo sapiens

689

&lt;400&gt; 716

Glu Gly Arg Glu Ala Gly Ser Gly Leu Ser Val Asp Ser Arg Asp Lys  
 1 5 10 15

Gly His Glu Gly Arg Gly Leu Gly Pro Phe Arg Ile Pro Gln Asp Ser  
 20 25 30

Gln Val Gln Leu Cys Gln Lys Gly Thr Phe His Val Met Gln Leu Arg  
 35 40 45

Gly Leu Ser Leu Asn Pro Arg Leu Leu Leu Thr Leu Gly Ser Phe Asn  
 50 55 60

Gln Val Gly Gln Pro Leu Leu Gln Arg Gly Val Gly Trp Leu Ser Ser  
 65 70 75 80

Leu Ser His Ala Ala Cys Glu Asp Arg Gly Gly Gly Val Gly Ser Gly  
 85 90 95

Lys Ser Pro Glu Asn Arg Arg Gly Ile  
 100 105

&lt;210&gt; 717

&lt;211&gt; 431

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 717

Arg Ala Ala Gly Ile Arg His Glu Arg Gly Gly Pro Thr Gly Ser Cys  
 1 5 10 15

Pro Gly Leu Pro Ser Pro Pro Met Val Leu Tyr Ile Lys Tyr Pro Gly  
 20 25 30

Trp Arg Ser His Met Leu Leu Thr Glu Gly Gly Asn Tyr His Ser Ser  
 35 40 45

Leu Gly Thr Arg Cys Glu Leu Ser Cys Asp Arg Gly Phe Arg Leu Ile  
 50 55 60

Gly Arg Arg Ser Val Gln Cys Leu Pro Ser Arg Arg Trp Ser Gly Thr  
 65 70 75 80

Ala Tyr Cys Arg Gln Met Arg Cys His Ala Leu Pro Phe Ile Thr Ser  
 85 90 95

Gly Thr Tyr Thr Cys Thr Asn Gly Val Leu Leu Asp Ser Arg Cys Asp  
 100 105 110

Tyr Ser Cys Ser Ser Gly Tyr His Leu Glu Gly Asp Arg Ser Arg Ile  
 115 120 125  
 Cys Met Glu Asp Gly Arg Trp Ser Gly Gly Glu Pro Val Cys Val Asp  
 130 135 140  
 Ile Asp Pro Pro Lys Ile Arg Cys Pro His Ser Arg Glu Lys Met Ala  
 145 150 155 160  
 Glu Pro Glu Lys Leu Thr Ala Arg Val Tyr Trp Asp Pro Pro Leu Val  
 165 170 175  
 Lys Asp Ser Ala Asp Gly Thr Ile Thr Arg Val Thr Leu Arg Gly Pro  
 180 185 190  
 Glu Pro Gly Ser His Phe Pro Glu Gly Glu His Val Ile Arg Tyr Thr  
 195 200 205  
 Ala Tyr Asp Arg Ala Tyr Asn Arg Ala Ser Cys Lys Phe Ile Val Lys  
 210 215 220  
 Val Gln Val Arg Arg Cys Pro Thr Leu Lys Pro Pro Gln His Gly Tyr  
 225 230 235 240  
 Leu Thr Cys Thr Ser Ala Gly Asp Asn Tyr Gly Ala Thr Cys Glu Tyr  
 245 250 255  
 His Cys Asp Gly Gly Tyr Asp Arg Gln Gly Thr Pro Ser Arg Val Cys  
 260 265 270  
 Gln Ser Ser Arg Gln Trp Ser Gly Ser Pro Pro Ile Cys Ala Pro Met  
 275 280 285  
 Lys Ile Asn Val Asn Val Asn Ser Ala Ala Gly Leu Leu Asp Gln Phe  
 290 295 300  
 Tyr Glu Lys Gln Arg Leu Leu Ile Ile Ser Ala Pro Asp Pro Ser Asn  
 305 310 315 320  
 Arg Tyr Tyr Lys Met Gln Ile Ser Met Leu Gln Gln Ser Thr Cys Gly  
 325 330 335  
 Leu Asp Leu Arg His Val Thr Ile Ile Glu Leu Val Gly Gln Pro Pro  
 340 345 350  
 Gln Glu Val Gly Arg Ile Arg Glu Gln Gln Leu Ser Ala Asn Ile Ile  
 355 360 365  
 Glu Glu Leu Arg Gln Phe Gln Arg Leu Thr Arg Ser Tyr Phe Asn Met  
 370 375 380



691

Val Leu Ile Asp Lys Gln Gly Ile Asp Arg Asp Arg Tyr Met Glu Pro  
 385 390 395 400

Val Thr Pro Glu Glu Ile Phe Thr Phe Ile Asp Asp Tyr Leu Leu Ser  
 405 410 415

Asn Gln Glu Leu Thr Gln Arg Arg Glu Gln Arg Asp Ile Cys Glu  
 420 425 430

&lt;210&gt; 718

&lt;211&gt; 417

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 718

Gln Gly Leu Pro Asp Gly Val Trp Ala His Gly Thr Cys Pro Gly His  
 1 5 10 15

Arg Leu Val Ser Ser Gln Arg Arg Ile Ile Ala Ser Gly Ser Glu Asp  
 20 25 30

Cys Thr Val Met Val Trp Gln Ile Pro Glu Asn Gly Leu Thr Ser Pro  
 35 40 45

Leu Thr Glu Pro Val Val Val Leu Glu Gly His Thr Lys Arg Val Gly  
 50 55 60

Ile Ile Ala Trp His Pro Thr Ala Arg Asn Val Leu Leu Ser Ala Gly  
 65 70 75 80

Cys Asp Asn Val Val Leu Ile Trp Asn Val Gly Thr Ala Glu Glu Leu  
 85 90 95

Tyr Arg Leu Asp Ser Leu His Pro Asp Leu Ile Tyr Asn Val Ser Trp  
 100 105 110

Asn His Asn Gly Ser Leu Phe Cys Ser Ala Cys Lys Asp Lys Ser Val  
 115 120 125

Arg Ile Ile Asp Pro Arg Arg Gly Thr Leu Val Ala Glu Arg Glu Lys  
 130 135 140

Ala His Glu Gly Ala Arg Pro Met Arg Ala Ile Phe Leu Ala Asp Gly  
 145 150 155 160

Lys Val Phe Thr Thr Gly Phe Ser Arg Met Ser Glu Arg Gln Leu Ala  
 165 170 175

692

Leu Trp Asp Pro Glu Asn Leu Glu Glu Pro Met Ala Leu Gln Glu Leu  
180 185 190

Asp Ser Ser Asn Gly Ala Leu Leu Pro Phe Tyr Asp Pro Asp Thr Ser  
195 200 205

Val Val Tyr Val Cys Gly Lys Gly Asp Ser Ser Ile Arg Tyr Phe Glu  
210 215 220

Ile Thr Glu Glu Pro Pro Tyr Ile His Phe Leu Asn Thr Phe Thr Ser  
225 230 235 240

Lys Glu Pro Gln Arg Gly Met Gly Ser Met Pro Lys Arg Gly Leu Glu  
245 250 255

Val Ser Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu His Glu Arg Lys  
260 265 270

Cys Glu Pro Ile Val Met Thr Val Pro Arg Lys Ser Asp Leu Phe Gln  
275 280 285

Asp Asp Leu Tyr Pro Asp Thr Ala Gly Pro Glu Ala Ala Leu Glu Ala  
290 295 300

Glu Glu Trp Val Ser Gly Arg Asp Ala Asp Pro Ile Leu Ile Ser Leu  
305 310 315 320

Arg Glu Ala Tyr Val Pro Ser Lys Gln Arg Asp Leu Lys Ile Ser Arg  
325 330 335

Arg Asn Val Leu Ser Asp Ser Arg Pro Ala Met Ala Pro Gly Ser Ser  
340 345 350

His Leu Gly Ala Pro Ala Ser Thr Thr Thr Ala Ala Asp Ala Thr Pro  
355 360 365

Ser Gly Ser Leu Ala Arg Ala Gly Glu Ala Gly Lys Leu Glu Glu Val  
370 375 380

Met Gln Glu Leu Arg Ala Leu Arg Ala Leu Val Lys Glu Gln Gly Asp  
385 390 395 400

Arg Ile Cys Arg Leu Glu Glu Gln Leu Gly Arg Met Glu Asn Gly Asp  
405 410 415

Ala

&lt;210&gt; 719

693

<211> 290  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (7)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (74)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (131)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 719

Glu Leu Ser Ala Ser Ala Xaa Asp Asp Gly Asn Phe Ser Leu Leu Ile  
1 5 10 15

Arg Ala Val Glu Glu Thr Asp Ala Gly Leu Tyr Thr Cys Asn Leu His  
20 25 30

His His Tyr Cys His Leu Tyr Glu Ser Leu Ala Val Arg Leu Glu Val  
35 40 45

Thr Asp Gly Pro Pro Ala Pro Pro Pro Thr Gly Thr Ala Arg Arg Arg  
50 55 60

Cys Trp Arg Trp Arg Ala Ala Pro Ala Xaa Leu Thr Cys Val Asn Arg  
65 70 75 80

Gly His Val Trp Thr Asp Arg His Val Glu Glu Ala Gln Gln Val Val  
85 90 95

His Trp Asp Arg Gln Pro Pro Gly Val Pro His Asp Arg Ala Asp Arg  
100 105 110

Leu Leu Asp Leu Tyr Ala Ser Ala Ser Ala Ala Leu Arg Ala Pro Phe  
115 120 125

Ser Ala Xaa Arg Val Ala Val Gly Ala Asp Ala Phe Lys Arg Gly Asp  
130 135 140

Phe Ser Leu Arg Ile Glu Pro Leu Glu Val Ala Asp Glu Gly Thr Tyr  
145 150 155 160

Ser Cys His Leu His His His Tyr Trp Arg Ala Ala Thr Thr Ser Ser

694

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<210> 720
<211> 459
<212> PRT
<213> Homo sapiens
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<220>  
<221> SITE  
<222> (50)  
<223> Xaa equals any of the naturally occurring L-amino acids
```

```

<400> 720
Asp Ala His Pro Lys Pro Cys Cys Glu Thr Ser Ala Ala Ala Cys Arg
 1             5             10             15
Leu Val Glu Arg Ile Leu Thr Ser Trp Glu Glu Asn Asp Arg Val Gln
          20             25             30
Cys Ala Gly Gly Pro Arg Lys Gly Tyr Met Gly His Leu Thr Arg Val
      35             40             45
Ala Xaa Ala Leu Val Gln Asn Thr Glu Lys Gly Pro Asn Ala Glu Gln
    50             55             60

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Leu Arg Gln Leu Leu Lys Glu Leu Pro Ser Glu Gln Gln Glu Gln Trp  
 65 70 75 80  
 Glu Ala Phe Val Ser Gly Pro Leu Ala Glu Thr Asn Lys Lys Asn Met  
 85 90 95  
 Val Asp Leu Val Asn Thr His His Leu His Ser Ser Ser Asp Asp Glu  
 100 105 110  
 Asp Asp Arg Leu Lys Glu Phe Asn Phe Pro Glu Glu Ala Val Leu Gln  
 115 120 125  
 Gln Ala Phe Met Asp Phe Gln Met Gln Arg Met Thr Ser Ala Phe Ile  
 130 135 140  
 Asp His Phe Gly Phe Asn Asp Glu Glu Phe Gly Glu Gln Glu Glu Ser  
 145 150 155 160  
 Val Asn Ala Pro Phe Asp Lys Thr Ala Asn Ile Thr Phe Ser Leu Asn  
 165 170 175  
 Ala Asp Asp Glu Asn Pro Asn Ala Asn Leu Leu Glu Ile Cys Tyr Lys  
 180 185 190  
 Asp Arg Ile Gln Gln Phe Asp Asp Asp Glu Glu Glu Glu Asp Glu Glu  
 195 200 205  
 Glu Ala Gln Gly Ser Gly Glu Ser Asp Gly Glu Asp Gly Ala Trp Gln  
 210 215 220  
 Gly Ser Gln Leu Ala Arg Gly Ala Arg Leu Gly Gln Pro Pro Gly Val  
 225 230 235 240  
 Arg Ser Gly Gly Ser Thr Asp Ser Glu Asp Glu Glu Glu Glu Asp Glu  
 245 250 255  
 Glu Glu Glu Glu Asp Glu Glu Gly Ile Gly Cys Ala Ala Arg Gly Gly  
 260 265 270  
 Ala Thr Pro Leu Ser Tyr Pro Ser Pro Gly Pro Gln Pro Pro Gly Pro  
 275 280 285  
 Ser Trp Thr Ala Thr Phe Asp Pro Val Pro Thr Asp Ala Pro Thr Ser  
 290 295 300  
 Pro Arg Val Ser Gly Glu Glu Glu Leu His Thr Gly Pro Pro Ala Pro  
 305 310 315 320  
 Gln Gly Pro Leu Ser Val Pro Gln Gly Leu Pro Thr Gln Ser Leu Ala  
 325 330 335

Ser Pro Pro Ala Arg Asp Ala Leu Gln Leu Arg Ser Gln Asp Pro Thr  
340 345 350

Pro Pro Ser Ala Pro Gln Glu Ala Thr Glu Gly Ser Lys Val Thr Glu  
355 360 365

Pro Ser Ala Pro Cys Gln Ala Leu Val Ser Ile Gly Asp Leu Gln Ala  
370 375 380

Thr Phe His Gly Ile Arg Ser Ala Pro Ser Ser Ser Asp Ser Ala Thr  
385 390 395 400

Arg Asp Pro Ser Thr Ser Val Pro Ala Ser Gly Ala His Gln Pro Pro  
405 410 415

Gln Thr Thr Glu Gly Glu Lys Ser Pro Glu Pro Leu Gly Leu Pro Gln  
420 425 430

Ser Gln Ser Ala Gln Ala Leu Thr Pro Pro Pro Ile Pro Asn Gly Ser  
435 440 445

Ala Pro Glu Gly Pro Ala Ser Pro Gly Ser Gln  
450 455

&lt;210&gt; 721

&lt;211&gt; 523

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (115)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (194)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (327)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

697

&lt;400&gt; 721

Leu Gln Arg Leu Lys Leu Ile Lys Pro Leu Leu Xaa Phe Glu Ser Leu  
 1 5 10 15

Glu Glu Cys Tyr Met Ala Lys Ile Leu Val Ala Glu Gly Thr Arg Asp  
 20 25 30

Val Pro Ile Gly Ala Ile Ile Cys Ile Thr Val Gly Lys Pro Glu Asp  
 35 40 45

Ile Glu Ala Phe Lys Asn Tyr Thr Leu Asp Ser Ser Ala Ala Pro Thr  
 50 55 60

Pro Gln Ala Ala Pro Ala Pro Thr Pro Ala Ala Thr Ala Ser Pro Pro  
 65 70 75 80

Thr Pro Ser Ala Gln Ala Pro Gly Ser Ser Tyr Pro Pro His Met Gln  
 85 90 95

Val Leu Leu Pro Ala Leu Ser Pro Thr Met Thr Met Gly Thr Val Gln  
 100 105 110

Arg Trp Xaa Lys Lys Val Gly Glu Lys Leu Ser Glu Gly Asp Leu Leu  
 115 120 125

Ala Glu Ile Glu Thr Asp Lys Ala Thr Ile Gly Phe Glu Val Gln Glu  
 130 135 140

Glu Gly Tyr Leu Ala Lys Ile Leu Val Pro Glu Gly Thr Arg Asp Val  
 145 150 155 160

Pro Leu Gly Thr Pro Leu Cys Ile Ile Val Glu Lys Glu Ala Asp Ile  
 165 170 175

Ser Ala Phe Ala Asp Tyr Arg Pro Thr Glu Val Thr Asp Leu Lys Pro  
 180 185 190

Gln Xaa Pro Pro Pro Thr Pro Pro Pro Val Ala Ala Val Pro Pro Thr  
 195 200 205

Pro Gln Pro Leu Ala Pro Thr Pro Ser Ala Pro Cys Pro Ala Thr Pro  
 210 215 220

Ala Gly Pro Lys Gly Arg Val Phe Val Ser Pro Leu Ala Lys Lys Leu  
 225 230 235 240

Ala Val Glu Lys Gly Ile Asp Leu Thr Gln Val Lys Gly Thr Gly Pro  
 245 250 255

Asp Gly Arg Ile Thr Lys Lys Asp Ile Asp Ser Phe Val Pro Ser Lys  
 260 265 270

Val Ala Pro Ala Pro Ala Ala Val Val Pro Pro Thr Gly Pro Gly Met  
275 280 285

Ala Pro Val Pro Thr Gly Val Phe Thr Asp Ile Pro Ile Ser Asn Ile  
290 295 300

Arg Arg Val Ile Ala Gln Arg Leu Met Gln Ser Lys Gln Thr Ile Pro  
305 310 315 320

His Tyr Tyr Leu Ser Ile Xaa Val Asn Met Gly Glu Val Leu Leu Val  
325 330 335

Arg Lys Glu Leu Asn Lys Ile Leu Glu Gly Arg Ser Lys Ile Ser Val  
340 345 350

Asn Asp Phe Ile Ile Lys Ala Ser Ala Leu Ala Cys Leu Lys Val Pro  
355 360 365

Glu Ala Asn Ser Ser Trp Met Asp Thr Val Ile Arg Gln Asn His Val  
370 375 380

Val Asp Val Ser Val Ala Val Ser Thr Pro Ala Gly Leu Ile Thr Pro  
385 390 395 400

Ile Val Phe Asn Ala His Ile Lys Gly Val Glu Thr Ile Ala Asn Asp  
405 410 415

Val Val Ser Leu Ala Thr Lys Ala Arg Glu Gly Lys Leu Gln Pro His  
420 425 430

Glu Phe Gln Gly Gly Thr Phe Thr Ile Ser Asn Leu Gly Met Phe Gly  
435 440 445

Ile Lys Asn Phe Ser Ala Ile Ile Asn Pro Pro Gln Ala Cys Ile Leu  
450 455 460

Ala Ile Gly Ala Ser Glu Asp Lys Leu Val Pro Ala Asp Asn Glu Lys  
465 470 475 480

Gly Phe Asp Val Ala Ser Met Met Ser Val Thr Leu Ser Cys Asp His  
485 490 495

Arg Val Val Asp Gly Ala Val Gly Ala Gln Trp Leu Ala Glu Phe Arg  
500 505 510

Lys Tyr Leu Glu Lys Pro Ile Thr Met Leu Leu  
515 520



699

<210> 722  
 <211> 111  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (10)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 722  
 Ser Ser Arg Ser Arg Ala Ala Asp Glu Xaa Ala Leu Cys Leu Gln Cys  
 1 5 10 15  
 Asp Met Asn Asp Cys Tyr Ser Arg Leu Arg Arg Leu Val Pro Thr Ile  
 20 25 30  
 Pro Pro Asn Lys Lys Val Ser Lys Val Glu Ile Leu Gln His Val Ile  
 35 40 45  
 Asp Tyr Ile Leu Asp Leu Gln Leu Ala Leu Glu Thr His Pro Ala Leu  
 50 55 60  
 Leu Arg Gln Pro Pro Pro Pro Ala Pro Pro His His Pro Ala Gly Thr  
 65 70 75 80  
 Cys Pro Ala Ala Pro Pro Arg Thr Pro Leu Thr Ala Leu Asn Thr Asp  
 85 90 95  
 Pro Ala Gly Ala Val Asn Lys Gln Gly Asp Ser Ile Leu Cys Arg  
 100 105 110

<210> 723  
 <211> 190  
 <212> PRT  
 <213> Homo sapiens

<400> 723  
 Ser Gly Gly Gly Gly Arg Met Ile Lys Leu Phe Ser Leu Lys Gln  
 1 5 10 15  
 Gln Lys Lys Glu Glu Glu Ser Ala Gly Gly Thr Lys Gly Ser Ser Lys  
 20 25 30  
 Lys Ala Ser Ala Ala Gln Leu Arg Ile Gln Lys Asp Ile Asn Glu Leu  
 35 40 45  
 Asn Leu Pro Lys Thr Cys Asp Ile Ser Phe Ser Asp Pro Asp Asp Leu  
 50 55 60

Leu Asn Phe Lys Leu Val Ile Cys Pro Asp Glu Gly Phe Tyr Lys Ser  
65 70 75 80

Gly Lys Phe Val Phe Ser Phe Lys Val Gly Gln Gly Tyr Pro His Asp  
85 90 95

Pro Pro Lys Val Lys Cys Glu Thr Met Val Tyr His Pro Asn Ile Asp  
100 105 110

Leu Glu Gly Asn Val Cys Leu Asn Ile Leu Arg Glu Asp Trp Lys Pro  
115 120 125

Val Leu Thr Ile Asn Ser Ile Ile Tyr Gly Leu Gln Tyr Leu Phe Leu  
130 135 140

Glu Pro Asn Pro Glu Asp Pro Leu Asn Lys Glu Ala Ala Glu Val Leu  
145 150 155 160

Gln Asn Asn Arg Arg Leu Phe Glu Gln Asn Val Gln Arg Ser Met Arg  
165 170 175

Gly Gly Tyr Ile Gly Ser Thr Tyr Phe Glu Arg Cys Leu Lys  
180 185 190

&lt;210&gt; 724

&lt;211&gt; 524

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (247)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (417)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (440)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (443)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

701

&lt;400&gt; 724

Arg Arg Arg Arg Ala Asp Arg Ala Thr Pro Arg Glu Val Leu Glu Thr  
 1 5 10 15  
 Pro Gly Ala Ala Ser Val Gln Thr Leu Pro Ser Val Thr Met Lys Leu  
 20 25 30  
 Trp Val Ser Ala Leu Leu Met Ala Trp Phe Gly Val Leu Ser Cys Val  
 35 40 45  
 Gln Ala Glu Phe Phe Thr Ser Ile Gly His Met Thr Asp Leu Ile Tyr  
 50 55 60  
 Ala Glu Lys Glu Leu Val Gln Ser Leu Lys Glu Tyr Ile Leu Val Glu  
 65 70 75 80  
 Glu Ala Lys Leu Ser Lys Ile Lys Ser Trp Ala Asn Lys Met Glu Ala  
 85 90 95  
 Leu Thr Ser Lys Ser Ala Ala Asp Ala Glu Gly Tyr Leu Ala His Pro  
 100 105 110  
 Val Asn Ala Tyr Lys Leu Val Lys Arg Leu Asn Thr Asp Trp Pro Ala  
 115 120 125  
 Leu Glu Asp Leu Val Leu Gln Asp Ser Ala Ala Gly Phe Ile Ala Asn  
 130 135 140  
 Leu Ser Val Gln Arg Gln Phe Phe Pro Thr Asp Glu Asp Glu Ile Gly  
 145 150 155 160  
 Ala Ala Lys Ala Leu Met Arg Leu Gln Asp Thr Tyr Arg Leu Asp Pro  
 165 170 175  
 Gly Thr Ile Ser Arg Gly Glu Leu Pro Gly Thr Lys Tyr Gln Ala Met  
 180 185 190  
 Leu Ser Val Asp Asp Cys Phe Gly Met Gly Arg Ser Ala Tyr Asn Glu  
 195 200 205  
 Gly Asp Tyr Tyr His Thr Val Leu Trp Met Glu Gln Val Leu Lys Gln  
 210 215 220  
 Leu Asp Ala Gly Glu Glu Ala Thr Thr Thr Lys Ser Gln Val Leu Asp  
 225 230 235 240  
 Tyr Leu Ser Tyr Ala Val Xaa Gln Leu Gly Asp Leu His Arg Ala Leu  
 245 250 255  
 Glu Leu Thr Arg Arg Leu Leu Ser Leu Asp Pro Ser His Glu Arg Ala

260 265 270  
Gly Gly Asn Leu Arg Tyr Phe Glu Gln Leu Leu Glu Glu Glu Arg Glu  
275 280 285  
Lys Thr Leu Thr Asn Gln Thr Glu Ala Glu Leu Ala Thr Pro Glu Gly  
290 295 300  
Ile Tyr Glu Arg Pro Val Asp Tyr Leu Pro Glu Arg Asp Val Tyr Glu  
305 310 315 320  
Ser Leu Cys Arg Gly Glu Gly Val Lys Leu Thr Pro Arg Arg Gln Lys  
325 330 335  
Arg Leu Phe Cys Arg Tyr His His Gly Asn Arg Ala Pro Gln Leu Leu  
340 345 350  
Ile Ala Pro Phe Lys Glu Glu Asp Glu Trp Asp Ser Pro His Ile Val  
355 360 365  
Arg Tyr Tyr Asp Val Met Ser Asp Glu Glu Ile Glu Arg Ile Lys Glu  
370 375 380  
Ile Ala Lys Pro Lys Leu Ala Arg Ala Thr Val Arg Asp Pro Lys Thr  
385 390 395 400  
Gly Val Leu Thr Val Ala Ser Tyr Arg Val Ser Lys Ser Ser Trp Leu  
405 410 415  
Xaa Glu Asp Asp Asp Pro Val Val Ala Arg Val Asn Arg Arg Met Gln  
420 425 430  
His Ile Thr Gly Leu Thr Val Xaa Thr Ala Xaa Leu Leu Gln Val Ala  
435 440 445  
Asn Tyr Gly Val Gly Gly Gln Tyr Glu Pro His Phe Asp Phe Ser Arg  
450 455 460  
Asn Asp Glu Arg Asp Thr Phe Lys His Leu Gly Thr Gly Asn Arg Val  
465 470 475 480  
Ala Thr Phe Leu Asn Tyr Met Ser Asp Val Glu Ala Gly Gly Ala Thr  
485 490 495  
Val Phe Pro Asp Leu Gly Ala Ala Ile Trp Pro Lys Lys Gly Thr Ala  
500 505 510  
Val Phe Trp Tyr Asn Leu Leu Arg Ser Gly Arg Arg  
515 520

703

&lt;210&gt; 725

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 725

Leu Lys Met Thr Ser Leu Phe Ala Gln Glu Ile Arg Leu Ser Lys Arg  
1 5 10 15

His Glu Glu Ile Val Ser Gln Arg Leu Met Leu Leu Gln Gln Met Glu  
20 25 30

Asn Lys Leu Gly Asp Gln His Thr Glu Lys Ala Ser Gln Leu Gln Thr  
35 40 45

Val Glu Thr Ala Phe Lys Arg Asn Leu Ser Leu Leu Lys Asp Ile Glu  
50 55 60

Ala Ala Glu Lys Ser Leu Gln Thr Arg Ile His Pro Leu Pro Arg Pro  
65 70 75 80

Glu Val Val Ser Leu Glu Thr Arg Tyr Trp Ala Ser  
85 90

&lt;210&gt; 726

&lt;211&gt; 690

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (108)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (123)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (383)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (688)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

<221> SITE

$\langle 222 \rangle$  (690)

<223> Xaa equals any of the naturally occurring L-amino acids

**<400> 726**

Val Ser Arg Ser Pro Arg Val Pro Leu Pro Pro Arg Ser Phe Ser Arg  
1 5 10 15

Met Ala Gly Asp Ser Thr Ala Thr Ser Arg Arg Leu Gly Ala Ala Pro  
20 25 30

Asp Arg Ala Ala Pro His Ile Leu Pro Ala Gly Ala His Arg Ala Ala  
35 40 45

Thr Ala Pro Gly Leu Gly Gly Gly Pro Glu Pro Leu Gly Arg Ala Leu  
50 55 60

Ala Gly Gly Leu Arg Gly Pro Gln Gly Asn Gly Trp Leu Gln Glu Arg  
65 70 75 80

Lys Arg Arg Cys Pro Gly Leu Ala Gly Cys Phe Glu Ala Ile Ser Cys  
85 90 95

Gly Thr Gly Leu Gly Leu Pro Gly Leu Ala Leu Xaa Arg Glu Leu Ile  
100 105 110

Ser Trp Gly Ala Pro Gly Ser Ala Asp Ser Xaa Arg Leu Leu His Trp  
115 120 125

Gly Ser His Pro Thr Ala Phe Val Val Ser Tyr Ala Ala Ala Leu Pro  
130 135 140

Ala Ala Ala Leu Trp His Lys Leu Gly Ser Leu Trp Val Pro Gly Gly  
145 150 155 160

Gln Gly Gly Ser Gly Asn Pro Val Arg Arg Leu Leu Gly Cys Leu Gly  
165 170 175

Ser Glu Thr Arg Arg Leu Ser Leu Phe Leu Val Leu Val Val Leu Ser  
180 185 190

Ser Leu Gly Glu Met Ala Ile Pro Phe Phe Thr Gly Arg Leu Thr Asp  
195 200 205

Trp Ile Leu Gln Asp Gly Ser Ala Asp Thr Phe Thr Arg Asn Leu Thr  
210 215 220

Leu Met Ser Ile Leu Thr Ile Ala Ser Ala Val Leu Glu Phe Val Gly  
225                      230                      235                      240

705

Asp Gly Ile Tyr Asn Asn Thr Met Gly His Val His Ser His Leu Gln  
 245 250 255  
 Gly Glu Val Phe Gly Ala Val Leu Arg Gln Glu Thr Glu Phe Phe Gln  
 260 265 270  
 Gln Asn Gln Thr Gly Asn Ile Met Ser Arg Val Thr Glu Asp Thr Ser  
 275 280 285  
 Thr Leu Ser Asp Ser Leu Ser Glu Asn Leu Ser Leu Phe Leu Trp Tyr  
 290 295 300  
 Leu Val Arg Gly Leu Cys Leu Leu Gly Ile Met Leu Trp Gly Ser Val  
 305 310 315 320  
 Ser Leu Thr Met Val Thr Leu Ile Thr Leu Pro Leu Leu Phe Leu Leu  
 325 330 335  
 Pro Lys Lys Val Gly Lys Trp Tyr Gln Leu Leu Glu Val Gln Val Arg  
 340 345 350  
 Glu Ser Leu Ala Lys Ser Ser Gln Val Ala Ile Glu Ala Leu Ser Ala  
 355 360 365  
 Met Pro Thr Val Arg Ser Phe Ala Asn Glu Glu Gly Glu Ala Xaa Lys  
 370 375 380  
 Phe Arg Glu Lys Leu Gln Glu Ile Lys Thr Leu Asn Gln Lys Glu Ala  
 385 390 395 400  
 Val Ala Tyr Ala Val Asn Ser Trp Thr Thr Ser Ile Ser Gly Met Leu  
 405 410 415  
 Leu Lys Val Gly Ile Leu Tyr Ile Gly Gly Gln Leu Val Thr Ser Gly  
 420 425 430  
 Ala Val Ser Ser Gly Asn Leu Val Thr Phe Val Leu Tyr Gln Met Gln  
 435 440 445  
 Phe Thr Gln Ala Val Glu Val Leu Leu Ser Ile Tyr Pro Arg Val Gln  
 450 455 460  
 Lys Ala Val Gly Ser Ser Glu Lys Ile Phe Glu Tyr Leu Asp Arg Thr  
 465 470 475 480  
 Pro Arg Cys Pro Pro Ser Gly Leu Leu Thr Pro Leu His Leu Glu Gly  
 485 490 495  
 Leu Val Gln Phe Gln Asp Val Ser Phe Ala Tyr Pro Asn Arg Pro Asp  
 500 505 510

Val Leu Val Leu Gln Gly Leu Thr Phe Thr Leu Arg Pro Gly Glu Val  
           515                                  520                                  525  
 Thr Ala Leu Val Gly Pro Asn Gly Ser Gly Lys Ser Thr Val Ala Ala  
           530                                  535                                  540  
 Leu Leu Gln Asn Leu Tyr Gln Pro Thr Gly Gly Gln Leu Leu Leu Asp  
           545                                  550                                  555                                  560  
 Gly Lys Pro Leu Pro Gln Tyr Glu His Arg Tyr Leu His Arg Gln Val  
                                   565                                  570                                  575  
 Ala Ala Val Gly Gln Glu Pro Gln Val Phe Gly Arg Ser Leu Gln Glu  
                                   580                                  585                                  590  
 Asn Ile Ala Tyr Gly Leu Thr Gln Lys Pro Thr Met Glu Glu Ile Thr  
           595                                  600                                  605  
 Ala Ala Ala Val Lys Ser Gly Ala His Ser Phe Ile Ser Gly Leu Pro  
           610                                  615                                  620  
 Gln Gly Tyr Asp Thr Glu Val Asp Glu Ala Gly Ser Gln Leu Ser Gly  
           625                                  630                                  635                                  640  
 Gly Gln Arg Gln Ala Val Ala Leu Ala Arg Ala Leu Ile Arg Lys Pro  
                                   645                                  650                                  655  
 Cys Val Leu Ile Leu Asp Asp Ala Thr Ser Ala Leu Asp Ala Asn Ser  
           660                                  665                                  670  
 Gln Leu Gln Val Glu Gln Leu Leu Tyr Glu Ser Pro Glu Arg Tyr Xaa  
           675                                  680                                  685  
 Arg Xaa  
           690

<210> 727

<211> 82

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (44)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE



&lt;222&gt; (73)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 727

Thr Pro Pro Leu Val Ser Ser Val Ala Ala Leu Asp Ser His Arg Ser  
1 5 10 15

Thr Asn Pro Ile Val Asn Ser Ala Cys Lys Gly Ser Arg Leu Cys Ala  
20 25 30

Pro Tyr Glu Asn Leu Met Pro Asp Asp Leu Arg Xaa Asn Ser Phe Ile  
35 40 45

Leu Lys Pro Pro Phe Thr Leu Gln Ser Val Glu Lys Leu Ser Ser Thr  
50 55 60

Lys Leu Val Pro Gly Ala Lys Asn Xaa Gly Asp Arg Cys Ser Arg Glu  
65 70 75 80

Arg Ser

&lt;210&gt; 728

&lt;211&gt; 600

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (11)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (479)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (550)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (588)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (590)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 728

Ser Arg Val Lys Pro Arg Val Arg Gly Thr Xaa Val Arg Thr Pro Gly  
 1 5 10 15  
 Ser Arg Arg Gly Arg His Gly Ala Val Pro Gly Asp Trp Glu Ala Ala  
 20 25 30  
 Ala Gln Ala Arg Gly Ala Gly Gln Arg Leu Pro Thr Pro Ser Glu Ile  
 35 40 45  
 Leu Ser Asn Ala Gly Leu Arg Phe Glu Val Val Pro Ser Lys Phe Lys  
 50 55 60  
 Glu Lys Leu Asp Lys Ala Ser Phe Ala Thr Pro Tyr Gly Tyr Ala Met  
 65 70 75 80  
 Glu Thr Ala Lys Gln Lys Ala Leu Glu Val Ala Asn Arg Leu Tyr Gln  
 85 90 95  
 Lys Asp Leu Arg Ala Pro Asp Val Val Ile Gly Ala Asp Thr Ile Val  
 100 105 110  
 Thr Val Gly Gly Leu Ile Leu Glu Lys Pro Val Asp Lys Gln Asp Ala  
 115 120 125  
 Tyr Arg Met Leu Ser Arg Leu Ser Gly Arg Glu His Ser Val Phe Thr  
 130 135 140  
 Gly Val Ala Ile Val His Cys Ser Ser Lys Asp His Gln Leu Asp Thr  
 145 150 155 160  
 Arg Val Ser Glu Phe Tyr Glu Glu Thr Lys Val Lys Phe Ser Glu Leu  
 165 170 175  
 Ser Glu Glu Leu Leu Trp Glu Tyr Val His Ser Gly Glu Pro Met Asp  
 180 185 190  
 Lys Ala Gly Gly Tyr Gly Ile Gln Ala Leu Gly Gly Met Leu Val Glu  
 195 200 205  
 Ser Val His Gly Asp Phe Leu Asn Val Val Gly Phe Pro Leu Asn His  
 210 215 220  
 Phe Cys Lys Gln Leu Val Lys Leu Tyr Tyr Pro Pro Arg Pro Glu Asp  
 225 230 235 240  
 Leu Arg Arg Ser Val Lys His Asp Ser Ile Pro Ala Ala Asp Thr Phe  
 245 250 255

Glu Asp Leu Ser Asp Val Glu Gly Gly Gly Ser Glu Pro Thr Gln Arg  
 260 265 270  
 Asp Ala Gly Ser Arg Asp Glu Lys Ala Glu Ala Gly Glu Ala Gly Gln  
 275 280 285  
 Ala Thr Ala Glu Ala Glu Cys His Arg Thr Arg Glu Thr Leu Pro Pro  
 290 295 300  
 Phe Pro Thr Arg Leu Leu Glu Leu Ile Glu Gly Phe Met Leu Ser Lys  
 305 310 315 320  
 Gly Leu Leu Thr Ala Cys Lys Leu Lys Val Phe Asp Leu Leu Lys Asp  
 325 330 335  
 Glu Ala Pro Gln Lys Ala Ala Asp Ile Ala Ser Lys Val Asp Ala Ser  
 340 345 350  
 Ala Cys Gly Met Glu Arg Leu Leu Asp Ile Cys Ala Ala Met Gly Leu  
 355 360 365  
 Leu Glu Lys Thr Glu Gln Gly Tyr Ser Asn Thr Glu Thr Ala Asn Val  
 370 375 380  
 Tyr Leu Ala Ser Asp Gly Glu Tyr Ser Leu His Gly Phe Ile Met His  
 385 390 395 400  
 Asn Asn Asp Leu Thr Trp Asn Leu Phe Thr Tyr Leu Glu Phe Ala Ile  
 405 410 415  
 Arg Glu Gly Thr Asn Gln His His Arg Ala Leu Gly Lys Lys Ala Glu  
 420 425 430  
 Asp Leu Phe Gln Asp Ala Tyr Tyr Gln Ser Pro Glu Thr Arg Leu Arg  
 435 440 445  
 Phe Met Arg Ala Met His Gly Met Thr Lys Leu Thr Ala Cys Gln Val  
 450 455 460  
 Ala Thr Ala Phe Asn Leu Ser Arg Phe Ser Ser Ala Cys Asp Xaa Gly  
 465 470 475 480  
 Gly Cys Thr Gly Ala Leu Ala Arg Glu Leu Ala Arg Glu Tyr Pro Arg  
 485 490 495  
 Met Gln Val Thr Val Phe Asp Leu Pro Asp Ile Ile Glu Leu Ala Ala  
 500 505 510  
 His Phe Gln Pro Pro Gly Pro Gln Gln Cys Arg Ser Thr Ser Gln Gln  
 515 520 525

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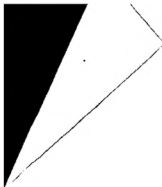
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